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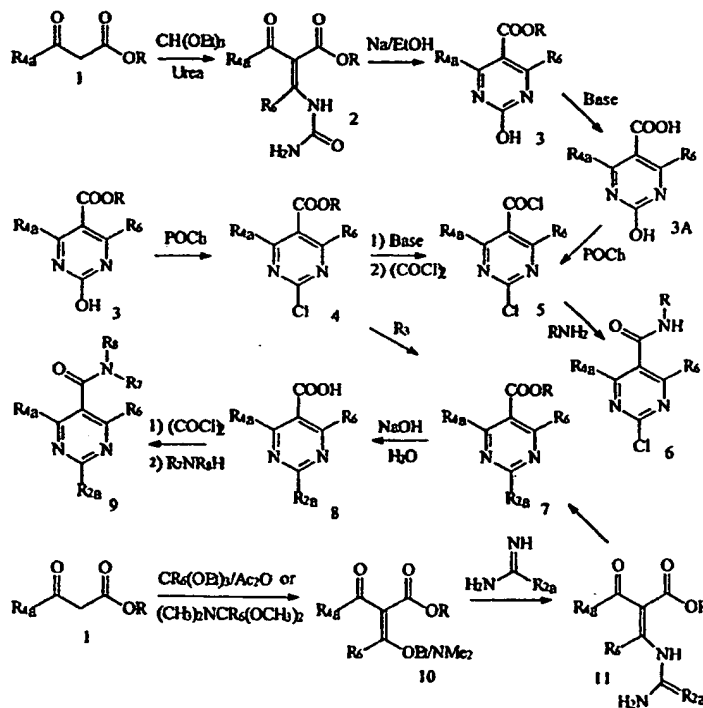
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## (54) Title: PYRIMIDINE CARBOXYAMIDES AND RELATED COMPOUNDS AND METHODS FOR TREATING INFLAMMATORY CONDITIONS

## (57) Abstract

Compounds having utility as anti-inflammatory agents in general and, more specifically, for the prevention and/or treatment of immuno-inflammatory and autoimmune diseases are disclosed. The compounds are pyrimidine- or pyrazine-containing compounds and, in one embodiment, are carboxyamides of the same. Methods are also disclosed for preventing and/or treating inflammatory conditions by administering to an animal in need thereof and effective amount of a compound of this invention, preferably in the form of a pharmaceutical composition.



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Description**PYRIMIDINE CARBOXAMIDES AND RELATED COMPOUNDS AND METHODS  
FOR TREATING INFLAMMATORY CONDITIONS**

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Technical Field

The present invention relates generally to compounds that block intracellular signal transduction and activation of transcription factors, and to methods for preventing or treating immunoinflammatory and autoimmune diseases.

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Background of the Invention

Signals necessary for cell growth, differentiation, response to bioregulatory molecules, infectious agents and physiological stress involve changes in the rates of gene expression. The ability to respond appropriately to such signaling events challenge the survival of the cell and ultimately the organism. Perturbations in the normal regulation of these specific genetic responses can result in pathogenic events which lead to acute and chronic disease.

In certain autoimmune diseases or chronic inflammatory states, continuous activation of T-cells eventually leads to a self-perpetuating destruction of normal tissues or organs. This is caused by the induction of adhesion molecules, chemotaxis of leukocytes, activation of leukocytes and the production of mediators of inflammation. All of these events are regulated at the level of transcription for the production of new proteins, including cytokines. The production of cytokines, as well as a number of other cellular regulators, is controlled by a family of proteins known as transcription factors (TFs). These transcription factors, when activated, bind to specific regions on the DNA and act as molecular switches or messengers to induce or upregulate gene expression. The activation of these TFs is caused by a variety of external signals including physiological stress, infectious agents and other bioregulatory molecules. Once the plasma membrane receptors are activated, a cascade of protein kinases and second messengers are induced which, in turn, result in the production of RNA transcripts. The end result is the production of proinflammatory proteins via translation and processing of the RNA transcripts.

This activation system can, at times, be very robust. For example, a specific set of external signals could result in a single transcription factor to induce many proteins responsible for a given disease. Therefore, regulating this process by disrupting

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the production of activated TF(s) has the potential to attenuate the production of the associated pathological proteins, thereby halting or reversing the course of the disease.

Two transcription factors, NF $\kappa$ B and AP-1, have been shown to regulate the production of many proinflammatory cytokines and related proteins that are elevated in immunoinflammatory diseases. These TFs regulate interleukin-1 (IL-1), interleukin-2 (IL-2), tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), interleukin-6 (IL-6) and interleukin-8 (IL-8) levels in a variety of cell types. For example, NF $\kappa$ B and other related complexes are involved in the rapid induction of genes whose products function in protective and proliferative responses upon exposure of cells to external stimuli. Similarly, AP-1 has a significant role in the regulation of interleukin-2 (IL-2) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) transcription during T-cell activation. In addition, TNF- $\alpha$  and IL-1 are strong activators of collagenase, gelatinase and stromelysin gene expression, which require a single AP-1 binding site in the promoter region of these genes. Therefore, an inhibitor of NF $\kappa$ B and/or AP-1 activation would coordinately repress the activities of a series of proteinases. In addition, cell adhesion molecules are also controlled by these TFs. All of these proteins have been shown to play a role in diseases, including osteoarthritis, transplant rejection, ischemia, reperfusion injury, trauma, certain cancers and viral disorders, and autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, psoriasis, inflammatory bowel disease, glomerulonephritis, lupus and juvenile diabetes. In summary, the role of these TFs is to act as a transducer for certain stimuli that lead to immune, inflammatory, and acute phase responses.

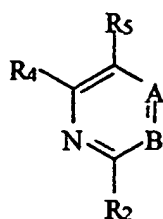
Since many diseases are caused by the inappropriate production of proteins, conventional therapeutic approaches have focused on inhibiting function or activity of individual effector proteins. These treatments have not always proved to be effective and, at times, are associated with many undesirable side effects. Therefore, there is a need for new therapies for the prevention and/or treatment of immunoinflammatory and autoimmune diseases. More specifically, there is a need for compounds that prevent, preferably by inhibiting transcription at an early stage, the production of proteins associated with immunoinflammatory and autoimmune diseases. Furthermore, these compounds should inhibit the kinase(s) that regulate the activation of TFs such as NF $\kappa$ B and AP-1. The present invention fulfills these needs and provides further related advantages.

#### Summary of the Invention

In brief, this invention is directed to compounds that block the activation of transcription factors (TFs), particularly NF $\kappa$ B and AP-1, and are believed to function

through inhibition of a family of specific kinases. This results in a decrease in a number of proinflammatory proteins, including IL-1, IL-2, IL-8 and/or  $\text{TNF}\alpha$ , which are responsible for tissue and organ damage associated with diseases such as rheumatoid arthritis, osteoarthritis, related autoimmune disorders and tissue rejection. Accordingly, compounds of the present invention are useful in, for example, the prevention of organ and tissue rejection associated with transplantation. Furthermore, the compounds of this invention also have utility in the prevention and/or treatment of immunoinflammatory and autoimmune diseases, as well as having general activity as anti-inflammatory agents.

In one embodiment of this invention, compounds are disclosed having the following general structure (I):



wherein A is  $\text{C-R}_6$  when B is N, and A is N when B is  $\text{C-R}_1$ , and wherein  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_4$ ,  $\text{R}_5$  and  $\text{R}_6$  are as defined in the following detailed description.

In another embodiment, a pharmaceutical composition is disclosed containing one or more compounds of this invention in combination with a pharmaceutically or prophylactically acceptable carrier or diluent.

In a further embodiment, methods are disclosed for preventing and/or treating inflammatory conditions by administering to a warm-blooded animal in need thereof an effective amount of a compound of this invention. Such inflammatory conditions include both immunoinflammatory conditions and autoimmune diseases. In the practice of the disclosed methods, the compounds are preferably administered to the warm-blooded animal in the form of a pharmaceutical composition.

These and other aspects of this invention will become evident upon reference to the attached figures and the following detailed description.

#### Brief Description of the Drawings

Figure 1 illustrates a reaction scheme for the synthesis of representative pyrimidine-containing compounds of this invention.

Figure 2 illustrates a reaction scheme for the synthesis of representative pyrazine-containing compounds of this invention.

Figure 3 illustrates the ability of a representative compound of this invention to inhibit the activation of NFκB and AP-1.

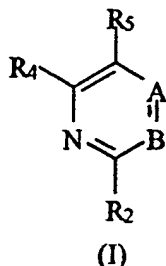
Figure 4 illustrates the ability of a representative compound of this invention to inhibit IL-2 and IL-8.

5 Figure 5 illustrates the ability of a representative compound of this invention to cause a dose-dependent suppression of alloantigen-induced PLN proliferation.

#### Detailed Description of the Invention

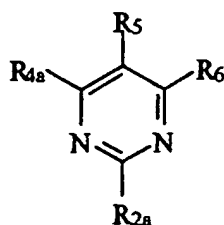
10 As mentioned above, the compounds of this invention block activation of transcription factors (TFs), and thus have utility as anti-inflammatory agents in general, and in the prevention and/or treatment of a variety of conditions, including (but not limited to) immunoinflammatory and autoimmune diseases. The compounds are believed to function by inhibiting, at an early stage, transcription of deleterious proteins  
 15 associated with such conditions or diseases. It is believed that this is achieved by inhibiting the kinase(s) that regulate the activation of TFs, such as NFκB and/or AP-1. By disrupting the production of these activated TFs, synthesis of pathological proteins, including proinflammatory cytokines, associated with a series of immunoinflammatory and autoimmune diseases are effectively blocked at a transcriptional level. Accordingly,  
 20 the compounds of this invention have activity in both the prevention and treatment of immunoinflammatory diseases such as rheumatoid arthritis, osteoarthritis and transplant rejection (tissue and organ), as well as autoimmune diseases such as multiple sclerosis.

The compounds of this invention are generally represented by the following general structure (I):

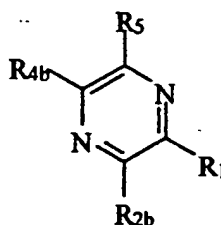


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wherein A is C-R<sub>6</sub> when B is N, and A is N when B is C-R<sub>1</sub>, and wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are as defined below. Thus, when A is C-R<sub>6</sub> and B is N, structure (I) is a pyrimidine-containing compound having structure (II), and when A is N and B is C-R<sub>1</sub>,  
 30 structure (I) is a pyrazine-containing compound having structure (III):

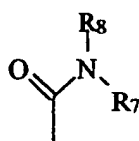


(II)

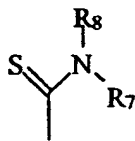


(III)

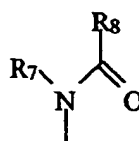
In structures (I), (II) and (III) above,  $R_3$  is selected from the following chemical moieties (i) through (iv):



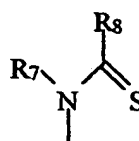
(i)



(ii)



(iii)



(iv)

wherein

$R_7$  is selected from hydrogen,  $-CH_3$  and  $-CH_2C_6H_5$ ; and

$R_8$  is selected from hydrogen and an unsubstituted or substituted  $C_{1-8}$ alkyl,  $C_{6-12}$ aryl,  $C_{7-12}$ aralkyl,  $C_{3-12}$ heterocycle and a  $C_{4-16}$ heterocyclealkyl.

The compounds of this invention further include pharmaceutically and prophylactically acceptable salts of compounds of structure (I). Compounds of structure (I) may contain proton donating groups (e.g., a carboxylic acid group) and/or proton accepting groups (e.g., a group with a nitrogen atom having a free lone pair of electrons, such as an amine group), and the salts of compounds of structure (I) may be formed and utilized in the practice of the invention. Thus, compounds of the invention may be in the form of a base addition salt (i.e., a salt of a proton donating group) or in the form of an acid addition salt (i.e., a salt of a proton accepting group), as well as the free acid or free base forms thereof.

Acid addition salts of a free base amino compound of the invention may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include acetic, ascorbic, benzenesulfonic, benzoic, fumaric, maleic, methanesulfonic, and succinic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric and nitric acids. Base addition salts of a free acid carboxylic acid compound of the invention may also be prepared by methods well known in the art, and may be formed from organic and inorganic bases. Thus, the compounds of this invention also include those salts derived from inorganic

bases such as the hydroxide or other salt of sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like, and organic bases such as substituted ammonium salts.

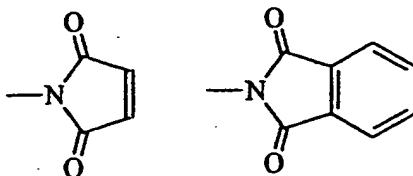
As used herein, the above terms have the following meaning:

5 A "C<sub>1-8</sub>alkyl" is a straight chain or branched, cyclic or non-cyclic, saturated or unsaturated carbon chain containing from 1 to 8 carbon atoms. In one embodiment, the C<sub>1-8</sub>alkyl is a fully saturated, straight chain alkyl selected from methyl, ethyl, n-propyl, n-butyl, n-pentyl and n-hexyl. In another embodiment, the C<sub>1-8</sub>alkyl is a fully saturated cyclic alkyl selected from (but not limited to) cyclopropyl, cyclobutyl, 10 cyclopentyl, cyclohexyl, methylenecyclopropyl and methylenecyclohexyl. In still a further embodiment, the C<sub>1-8</sub>alkyl is a fully saturated, branched alkyl selected from (but not limited to) isopropyl, sec-butyl, isobutyl, tert-butyl, isopentyl and isohexyl. In yet a further embodiment, the C<sub>1-8</sub>alkyl is an unsaturated straight chain alkyl selected from (but not limited to) ethylenyl, propylenyl, 1-butenyl, 1-pentenyl and 1-hexenyl.

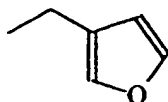
15 A "C<sub>6-12</sub>aryl" is an aromatic moiety containing from 6 to 12 carbon atoms. In one embodiment, the C<sub>6-12</sub>aryl is selected from (but not limited to) phenyl, tetralinyl, and naphthalenyl. In a preferred embodiment, the C<sub>6-12</sub>aryl is phenyl.

A "C<sub>7-12</sub>aralkyl" is an arene containing from 7 to 12 carbon atoms, and has both aliphatic and aromatic units. In one embodiment, the C<sub>7-12</sub>aralkyl is selected 20 from (but not limited to) benzyl, ethylbenzyl, propylbenzyl and isobutylbenzyl.

A "C<sub>3-12</sub>heterocycle" is a compound that contains a ring made up of more than one kind of atom, and which contains 3 to 12 carbon atoms. In one embodiment, the C<sub>3-12</sub>heterocycle is selected from (but not limited to) pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyrrolidinyl, pyridinyl, pyrimidinyl and purinyl. 25 In a further embodiment, the C<sub>3-12</sub>heterocycle includes the following structures:



A "C<sub>4-16</sub>heterocyclealkyl" is a compound that contains a C<sub>3-12</sub>heterocycle linked to a C<sub>1-8</sub>alkyl. In one embodiment, the C<sub>4-16</sub>heterocyclealkyl is a methylene furan having the following structure:





A "substituted" C<sub>1-8</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl, C<sub>3-12</sub>heterocycle or C<sub>4-16</sub>heterocyclealkyl is a C<sub>1-8</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl, C<sub>3-12</sub>heterocycle or C<sub>4-16</sub>heterocyclealkyl having one or more hydrogens replaced with a substituent selected from halogen (including -F, -Cl, -Br and -I), -OH, -R, -OR, -COOH, -COOR, -COR, -CONH<sub>2</sub>, -NH<sub>2</sub>, -NHR, -NRR, -SH, -SR, -SOOR, -SO<sub>3</sub>R and -SOR, where each occurrence of R is independently selected from an unsubstituted or substituted C<sub>1-8</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl, C<sub>3-12</sub>heterocycle or C<sub>4-16</sub>heterocyclealkyl as defined above. In one embodiment, the substituted C<sub>1-8</sub>alkyl is a C<sub>1-8</sub>haloalkyl including (but not limited to) -CF<sub>3</sub> and -C<sub>2</sub>F<sub>5</sub>.

10 In structure (II) above, R<sub>2a</sub> is selected from halogen, an unsubstituted or substituted C<sub>1-8</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl, C<sub>3-12</sub>heterocycle or C<sub>4-16</sub>heterocyclealkyl, -CN, -OR, -NHR, -NRR and -NRNCOR, wherein each occurrence of R is independently selected from an unsubstituted or substituted C<sub>1-8</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl, C<sub>3-12</sub>heterocycle or C<sub>4-16</sub>heterocyclealkyl as defined above. In one embodiment, R<sub>2a</sub> is selected from -Cl, -F, -CN and -CF<sub>3</sub>.

In structure (III) above, R<sub>2b</sub> is halogen, such as -Cl or -F.

In structure (II) above, R<sub>4a</sub> is selected from hydrogen, halogen, an unsubstituted or substituted C<sub>1-8</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl, C<sub>3-12</sub>heterocycle or C<sub>4-16</sub>heterocyclealkyl, -CN, -OR, -NHR, -NRR and -NRNCOR, wherein each occurrence of R is independently selected from an unsubstituted or substituted C<sub>1-8</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl, C<sub>3-12</sub>heterocycle or C<sub>4-16</sub>heterocyclealkyl as defined above. In one embodiment, R<sub>4a</sub> is selected from hydrogen, -CH<sub>3</sub>, -CF<sub>3</sub>, -C<sub>2</sub>F<sub>5</sub>, -C<sub>2</sub>H<sub>5</sub>, -C<sub>6</sub>H<sub>5</sub> and -CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>.

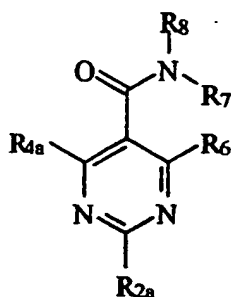
25 In structure (III) above, R<sub>4b</sub> is selected from hydrogen, halogen, -CN, and an unsubstituted or substituted C<sub>1-8</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl, C<sub>3-12</sub>heterocycle or C<sub>4-16</sub>heterocyclealkyl.

In structures (I) and (II) above, R<sub>6</sub> is selected from hydrogen, halogen, and an unsubstituted or substituted C<sub>1-8</sub>alkyl, including (but not limited to) a C<sub>1-8</sub>haloalkyl (such as -CF<sub>3</sub> and -C<sub>2</sub>F<sub>5</sub>). In one embodiment, R<sub>6</sub> is selected from hydrogen, -Cl, -F, -CH<sub>3</sub> and -CF<sub>3</sub>.

30 In structures (I) and (III) above, R<sub>1</sub> is selected from hydrogen, -CH<sub>3</sub>, -CF<sub>3</sub> and -C<sub>2</sub>H<sub>5</sub>.

In one embodiment, the compounds of this invention have structure (II) above, wherein R<sub>1</sub> is the chemical moiety (i). In this embodiment, the compounds disclosed herein have the following structure (IV):

8



(IV)

where  $R_{2a}$ ,  $R_{4a}$ ,  $R_6$ ,  $R_7$  and  $R_8$  are as defined above. In a preferred embodiment, representative compounds of structure (IV) contain  $R_{2a}$ ,  $R_{4a}$ ,  $R_6$ ,  $R_7$  and  $R_8$  moieties as identified in Table 1 below.

Table 1

Compounds of Structure (IV)

$R_{2a}$	$R_{4a}$	$R_6$	$R_7$	$R_8$
-Cl	-CF <sub>3</sub>	-H	-H	
-OCH <sub>3</sub>	-Cl	-CF <sub>3</sub>	-CH <sub>3</sub>	
-H	-F	-CH <sub>3</sub>		
-N(CH <sub>3</sub> ) <sub>2</sub>	-CH <sub>3</sub>	-Cl		
-CF <sub>3</sub>	-H			
-CN	-C <sub>2</sub> F <sub>5</sub>			
-NHNH <sub>2</sub>				
-NHPH				

wherein X, Y and Z are the same or different, and independently selected from hydrogen, -OH, -R, -OR, -COOH, -COOR, -COR, -CONH<sub>2</sub>, -NH<sub>2</sub>, -NHR, -NRR, -SH, -SR, -SOOR, -SO<sub>3</sub>R and -SOR, where each occurrence of R is independently selected from an unsubstituted or substituted C<sub>1-8</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl, C<sub>3-12</sub>heterocycle or C<sub>4-16</sub>heterocyclealkyl.

In a preferred embodiment of the compounds disclosed in Table 1 above, X, Y and Z are the same or different, and independently selected from -H, -Cl, -F, -CF<sub>3</sub>, -OH, -CH<sub>3</sub> and -OCH<sub>3</sub>. In a further preferred embodiment, R<sub>8</sub> is a 3,5-bis(trifluoromethyl)phenyl moiety or a 3-trifluoromethyl-5-halo-phenyl moiety.

As mentioned above, in one embodiment of this invention the compounds have structure (II). Within one aspect of this embodiment, R<sub>4</sub> is -CF<sub>3</sub> and R<sub>2</sub> is -Cl. Such compounds include (but are not limited to): 2-chloro-4-trifluoromethyl-5-N-(3',5'-bistrifluoromethylphenyl)pyrimidine carboxamide; 2-chloro-4-trifluoromethyl-5-N-(3',5'-dichlorophenyl)pyrimidine carboxamide; 2-chloro-4-trifluoromethyl-5-N-(4'-trifluoromethylphenyl)pyrimidine carboxamide; 2-chloro-4-trifluoromethyl-5-N-(phenyl)pyrimidine carboxamide; 2-chloro-4-trifluoromethyl-5-N-(cyclohexyl)pyrimidine carboxamide; 2-chloro-4-trifluoromethyl-5-N-(3',4',5'-trichlorophenyl)pyrimidine carboxamide; 2-chloro-4-trifluoromethyl-5-N-(benzyl)pyrimidine carboxamide; 2-chloro-4-trifluoromethyl-5-N-(4'-(2',1',3'-benzothiadiazole))pyrimidine carboxamide; 2-chloro-4-trifluoromethyl-5-N-(3',5'-dichloro-6'-hydroxyphenyl)pyrimidine carboxamide; 2-chloro-4-trifluoromethyl-5-N-(5'-(3'-methylisoxazole))pyrimidine carboxamide; 2-chloro-4-trifluoromethyl-5-N-(3'-N-acyl-4'-fluoroaniline)pyrimidine carboxamide; 2-chloro-4-trifluoromethyl-5-N-(3-trifluoromethyl-5'-ethoxycarbonylphenyl)pyrimidine carboxamide; 2-chloro-4-trifluoromethyl-5-N-(3'-trifluoromethyl-5-(carboxamide)phenyl) pyrimidine carboxamide; 2-chloro-4-trifluoromethyl-5-N-(3',5'-dichlorophenyl)-N-(methyl)pyrimidine carboxamide; and 2-chloro-4-trifluoromethyl-5-N-(3',5'-dichlorophenyl)-N-(benzyl)pyrimidine carboxamide.

Within another aspect of this embodiment, R<sub>4</sub> is -CF<sub>3</sub> and R<sub>2</sub> is a moiety other than -Cl. Such compounds include (but are not limited to): 2-fluoro-4-trifluoromethyl-5-N-(3',5'-bistrifluoromethyl)pyrimidine carboxamide, 5-(3',5'-bis(trifluoromethyl)phenacyl)-2-methoxy-4-trifluoromethylpyrimidine; 4-trifluoromethyl-5-N-(3',5'-dichlorophenyl)pyrimidine carboxamide; 2-dimethylamino-4-trifluoromethyl-5-N-(3',5'-dichlorophenyl)pyrimidine carboxamide; 2-triethylammonium chloride-4-trifluoromethyl-5-N-(3',5'-dichlorophenyl)pyrimidine carboxamide; 2-cyano-4-trifluoromethyl-5-N-[3',5'-(bistrifluoromethyl)phenyl]pyrimidine carboxamide; 2-hydrazino-4-trifluoromethyl-5-[N-(3',5'-dichlorophenyl)pyrimidine-5-carboxamide]; 2-[N-(1-Aminocitraconamide)]-4-trifluoromethyl-5-[N-(3',5'-dichlorophenyl) pyrimidine-5-carboxamide]; and 2-aminophenyl-4-trifluoromethyl-N-(3',5'-dichlorophenyl)pyrimidine-5-carboxamide.

Within yet a further aspect of this embodiment,  $R_{2a}$  is -Cl and  $R_{4a}$  is a moiety other than -CF<sub>3</sub>. Such compounds include (but are not limited to): 5-N-(3',5'-bis(trifluoromethyl)phenyl)-2,4-dichloro-6-methyl-pyrimidine carboxamide; 2-chloro-4-methyl-5-N-(3',5'-(bistrifluoromethyl)phenyl)pyrimidine carboxamide; 2,4-dichloro-5-N-(3',5'-bis(trifluoromethyl)benzyl)pyrimidine-5-carboxamide; and 2-chloro-4-phenyl-5-N-(3',5'-(bistrifluoromethyl)phenyl)pyrimidine carboxamide.

In another embodiment, the compounds of this invention have structure (III) above. Within one aspect of this embodiment,  $R_1$  is selected from hydrogen, -CH<sub>3</sub> and -CF<sub>3</sub>. Such compounds include (but are not limited to) pyrazine-containing compounds which correspond to the pyrimidine-containing compounds disclosed above. In one embodiment of structure (III),  $R_{2b}$  is -Cl,  $R_{4b}$  is -CF<sub>3</sub> and  $R_5$  is a moiety of structure (i) above.

A small number of compounds which fall within structure (I) above have been previously disclosed and/or are commercially available. However, such compounds have not been associated with the utilities of the present invention, or possess no recognized utility. Accordingly, compounds that fall within the scope of structure (I), and which have recognized utility, are specifically excluded from the novel compounds of structure (I). However, to the extent such compounds have not been disclosed for the utilities of the present invention, they are included in the various methods of this invention.

To this end, the novel compounds of this invention do not include compounds of structure (IV) above where  $R_7$  and  $R_8$  are both hydrogen, and where  $R_{2a}$  is selected from an unsubstituted, straight chain or branched, non-cyclic, saturated C<sub>1-3</sub> alkyl (*i.e.*, -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub> and -CH(CH<sub>3</sub>)<sub>2</sub>), -N(CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub> and -OR, where R is as defined above. Similarly, the novel compounds of structure (IV) are subject to the following provisos: (a) when  $R_{2a}$  is -Cl and  $R_6$  is -H,  $R_{4a}$  is not -CF<sub>3</sub>, -Cl, -CH<sub>3</sub> or -C(CH<sub>3</sub>)<sub>3</sub>, (b) when  $R_{2a}$  is -Cl and both  $R_{4a}$  and  $R_6$  are -H,  $R_8$  is not -CH(CN)C<sub>6</sub>H<sub>5</sub> or -(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>, and (c) when  $R_{2a}$  is -Cl and  $R_{4a}$  is -Cl,  $R_6$  is not -Cl or -CH<sub>2</sub>Cl.

The novel compounds of this invention also do not include compounds of structure (II) when  $R_5$  is moiety (iii) and (a)  $R_{2a}$  is -CH<sub>3</sub>, -OCH<sub>3</sub> or -N(CH<sub>3</sub>)<sub>2</sub>, or (b)  $R_8$  is -H or -CH<sub>3</sub>.

Furthermore, the novel compounds of structure (III) when  $R_5$  is moiety (i) are subject to the following proviso: when  $R_{2b}$  is -Cl,  $R_{4b}$  and  $R_1$  are not both hydrogen.

The compounds of this invention may be made by one skilled in organic synthesis by known techniques, as well as by the synthetic routes disclosed herein. For purpose of convenience, the compounds have been separated into pyrimidine-containing (structure (II)) and pyrazine-containing (structure (III)) compounds as set forth below.

- 5 The pyrimidine-containing compounds of this invention may be prepared as illustrated by the reaction scheme of Figure 1. In general, commercially available  $\beta$ -keto esters 1 are heated at elevated temperatures (75-110°C) with a mixture of urea and triethylorthoformate (or a substituted orthoformate) to provide ureido derivatives 2. Treatment of these intermediates with sodium alkoxides, such as sodium ethoxide in an  
10 alcoholic solvent at 35-100°C, gives 2-hydroxypyrimidine esters 3 which, upon treatment with a chlorinating agent such as phosphorous oxychloride at elevated temperatures (75-120°C), yields 2-chloropyrimidine esters 4. The 2-hydroxypyrimidine esters 3 may also be treated with a mild base, such as lithium hydroxide, sodium hydroxide or potassium carbonate to provide the corresponding acid 3A, which may  
15 then be converted with a chlorinating agent, such as phosphorous oxychloride or thionyl chloride in an inert solvent or neat at 25-75°C, to the acid chloride 5. Compounds of structure 6 may be prepared using standard conditions known in the art by reacting the acid chloride 5 with an amine in the presence of a base, such as potassium carbonate or dimethylaminopyridine (DMAP), in a non-protic solvent, such as methylene chloride or  
20 EtOAc at 25-40°C, followed by standard workup.

- Alternatively, pyrimidine-containing compounds of this invention may also be made by the following combinatorial procedure. Commercially available and/or readily synthesized amines, anilines and related compounds may be reacted with the acid chloride 5 in EtOAc in the presence of basic Amberlyst 21 resin. The reactions are  
25 quenched with 50  $\mu$ L of water and the final products are obtained in the organic layer and concentrated. This procedure may be done in a 96 well (1 mL deep well) plate and the final products isolated as dry powders. TLC analysis is performed on each compound and indicates the purity, and GC/MS and HPLC analysis demonstrates that the desired products are synthesized (mass spectral analysis, molecular weight) and are  
30 greater than 80% pure. By this method, eighty distinct pyrimidine-containing compounds may be routinely synthesized at the same time in one 96 well plate.

- In addition, compound 4 may be reacted with various nucleophiles in an aprotic solvent and at ambient temperature to provide derivatives 7. These compounds can be hydrolyzed with base to yield compounds having structure 8. Compounds of  
35 structure 8 can be converted to the acid chloride as described above, and reacted with various amines to give compounds having structure 9 using known conditions, including

the combinatorial approach described above. Alternatively, compounds of structure 7 can also be prepared by reacting the  $\beta$ -keto ester 1 in a sequential fashion with triethylorthoformate and acetic anhydride or N,N-dimethylformamide dimethyl acetal in DMF to give intermediate 10. Reacting intermediate 10 with a variety of amidines in alcoholic solvents provides intermediate 11 which, upon addition of base, provides compounds of structure 7.

Pyrazine-containing compounds of structure (III) may be prepared as illustrated by the reaction scheme of Figure 2. The synthesis of these compounds may begin with readily available pyruvic acid derivatives 12. These compounds are condensed with commercially available 2-cyano-1,2-diamino-2-substituted ethenes 13 in an alcoholic solvent (such as MeOH) in the presence of an acid (such as HCl) at ambient temperatures (25-60°C) to provide the cyano pyrazines of structure 14. The pyrazines may then be converted to the corresponding carboxylic acids 15 using a strong base such as sodium hydroxide in water, or a strong acid such as HCl, at elevated temperatures (70-110°C). These carboxylic acids may then be converted to 5-chloro-2-carbonyl acid chloride derivatives 16 using a chlorinating agent such as POCl<sub>3</sub> or SOCl<sub>2</sub>. Treatment of 16 with various amines or anilines at ambient temperatures in an inert solvent such as EtOAc or CH<sub>2</sub>Cl<sub>2</sub> provides compounds of structure 17.

The carboxylic acids of structure 15 can also be converted to the hydroxy ester 18 by treatment with SOCl<sub>2</sub> and MeOH at a temperature of 25-60°C. Treatment of 18 with a chlorinating agent such as SOCl<sub>2</sub> or POCl<sub>3</sub> in the presence of DMF gives the chloro ester 19. Compound 19 can also be converted to the acid chloride 16 using a mild base such as potassium carbonate in an aprotic solvent such as MeOH, followed by treatment with a chlorinating agent such as oxalyl chloride in an inert solvent such as methylene chloride at ambient temperatures.

The pyrazine-containing compounds of this invention may also be synthesized by appropriate combinatorial techniques as described. In short, commercially available and/or readily synthesized amines, anilines and related compounds may be reacted with the acid chloride 16 in EtOAc in the presence of basic Amberlyst 21 resin. The reactions are quenched with 50  $\mu$ L of water and the final products are obtained in the organic layer and concentrated. This procedure may be done in a 96 well (1 mL deep well) plate and the final products isolated as dry powders. TLC analysis is performed on each compound and indicates the purity, and GC and HPLC analysis demonstrates that the desired products are synthesized (mass spectral analysis, molecular weight) and are greater than 80% pure. By this method, eighty pyrazine-containing compounds may be routinely synthesized in one 96 well plate.

Once synthesized, the compounds of this invention may be formulated for administration to a warm-blooded animal by a variety of techniques known to those skilled in the art. In one embodiment, the compound is in the form of a pharmaceutical composition for prophylactic or therapeutic use, and which contains at least one  
5 compound of this invention in combination with a pharmaceutically acceptable carrier or diluent. The compound is present in the composition in an amount which, upon administration to the animal, is effective in preventing or treating the condition of interest. Preferably, the composition includes a compound of this invention in an amount ranging from 0.01 mg to 250 mg per dosage, depending upon the route of  
10 administration, and more preferably from 1 mg to 60 mg. Appropriate concentrations, dosages and modes of administration may be readily determined by one skilled in the art.

Suitable carriers or diluents are familiar to those skilled in the formulation field. For compositions formulated as liquid solutions, acceptable carrier or diluents include saline and sterile water, and may optionally include antioxidants, buffers,  
15 bacteriostats and other common additives. The compositions of this invention may also be formulated as pills, capsules, granules or tablets which contain, in addition to the compound of this invention, diluents, dispersing and surface active agents, binders and lubricants. One skilled in the art may further formulate the compounds of this invention in any appropriate manner, and in accordance with accepted practices, such as those  
20 disclosed in *Remington's Pharmaceutical Sciences*, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1990 (incorporated herein by reference).

In another embodiment, the present invention provides methods for preventing or treating a variety of conditions. Such methods include administering a compound of this invention to a warm-blooded animal in need thereof in an amount  
25 sufficient to prevent or treat the condition. Such methods include systemic administration of a compound of this invention, preferably in the form of a composition as disclosed above. As used herein, systemic administration includes oral and parental methods of administration. For oral administration, suitable pharmaceutical compositions include powders, granules, pills, tablets and capsules, as well as liquids,  
30 syrups, suspensions and emulsions. These compositions may also include flavorants, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable additives. For parental administration, the compounds of the present invention may be prepared in aqueous injectable solutions which may contain, in addition to the compound of this invention, buffers, antioxidants, bacteriostats and other additives  
35 commonly employed in such solutions.

As mentioned above, compounds of the present invention can be used to prevent or treat a wide variety of disorders, diseases and/or illnesses. In particular, the compounds may be administered to a warm-blooded animal for prevention or treatment of rheumatoid arthritis, osteoarthritis, tissue and/or organ transplant rejection, sepsis, ARDS, asthma, trauma, oxidative stress, cell death, irradiation damage, ischemia, reperfusion, cancer, viral infection, and autoimmune diseases such as psoriasis, inflammatory bowel disease, glomerulonephritis, lupus, uveitis and chronic hepatitis.

Compounds of this invention may be screened by known and accepted techniques for their ability to function as prophylactically and/or therapeutically active agents. For example, the compounds may be evaluated in *in vitro* and/or *in vivo* assays indicative of the compound's antiinflammatory and immunosuppressive properties. To this end, such compounds may first be evaluated in a number of cell-based assays which determine the ability of a compound to prevent activation of NF $\kappa$ B and AP-1 (see Example 56). Next, the compound's ability to attenuate cytokine levels (such as IL-2 and IL-8), which are known to be elevated in certain disease states, may be determined (see Example 57). The compounds may then be evaluated in an appropriate animal model, including rodent models of inflammation and immunosuppression (see Example 58).

It should be recognized that, for example, in the case of immunosuppressive drugs and other agents which have utility for the treatment of rheumatoid arthritis (RA), numerous studies have been performed directed to the activity of such drugs. To this end, cyclosporin A has been used in clinical trials since the late 1970's as a second-line drug and is recommended to be used only in patients with active RA. Thus, Experiment 58 was performed utilizing cyclosporin A as a positive control. A recent review of such immunosuppressive drugs, including relevant assays for the same, is presented by R.P. Carlson in *Exp. Opin. Invest. Drugs* 4(9):853-859, 1995 (incorporated herein by reference in its entirety, including cited references).

The following examples are presented for purpose of illustration, not limitation.

## EXAMPLES

To summarize the examples that follow, Examples 1-54 disclose the synthesis of representative compounds of this invention, as well as intermediates thereof; Example 55 discloses the synthesis of representative compounds by combinational chemistry techniques; Examples 56-57 disclose the ability of representative compounds of this invention to inhibit NF $\kappa$ B, AP-1 and cytokines; and Example 58 discloses the



activity of a representative compound of this invention in both graft versus host disease and contact sensitivity models.

Example 1

5                   2-CHLORO-4-TRIFLUOROMETHYL-5-N-  
                  [3',5'-BIS(TRIFLUOROMETHYL)PHENYL]PYRIMIDINE CARBOXAMIDE

To a mixture of 3,5-bistrifluoromethylaniline (0.20 g, 0.92 mmol), Amberlyst A-21 ion exchange resin (0.02 g) in EtOAc (5 mL) was added a solution of 2-chloro-4-trifluoromethylpyrimidine-5-carbonyl chloride (0.27 g, 1.13 mmol) in EtOAc  
10 (5 mL). The mixture was stirred for 0.5 h, then quenched with water (0.20 mL). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and the solvent removed under reduced pressure. The resulting oil was recrystallized from EtOH/H<sub>2</sub>O to provide the title compound (0.21 g, 53% yield) as a white solid; m.p. 162-163°C.

Example 2

15                   2-CHLORO-4-TRIFLUOROMETHYL-5-N-  
                  (4'-TRIFLUOROMETHYLPHENYL)PYRIMIDINE CARBOXAMIDE

The title compound was prepared as described in Example 1, but employing 4-trifluoromethylaniline (0.1 g, 0.41 mmol) in place of 3,5-bistrifluoromethylaniline and the acid chloride (0.10 g, 0.41 mmol), resulting in a 24%  
20 yield; m.p. 172-173°C.

Example 3

25                   2-CHLORO-4-TRIFLUOROMETHYL-  
                  5-N-(PHENYL)PYRIMIDINE CARBOXAMIDE

The title compound was prepared as described in Example 1, but employing aniline (0.04 g, 0.39 mmol) and the acid chloride (0.22 g, 0.90 mmol), resulting in a 62% yield; m.p. 108-181°C.

Example 4

30                   2-CHLORO-4-TRIFLUOROMETHYL-  
                  5-N-(CYCLOHEXYL)PYRIMIDINE CARBOXAMIDE

The title compound was prepared as described in Example 1, but employing cyclohexylamine (0.02 g, 0.18 mmol) and the acid chloride (0.05 g,  
35 0.22 mmol), resulting in a 33% yield; m.p. 150-151°C.

Example 52-CHLORO-4-TRIFLUOROMETHYL-  
5-N-(BENZYL)PYRIMIDINE CARBOXAMIDE

5 The title compound was prepared as described above in Example 1, but employing benzylamine (0.09 g, 0.92 mmol) and the acid chloride (0.25 g, 1.0 mmol), resulting in a 78% yield; m.p. 152-153°C.

Example 62-CHLORO-4-TRIFLUOROMETHYL-5-N-(3',4',5'-  
10 TRICHLOROPHENYL)PYRIMIDINE CARBOXAMIDE

The title compound was prepared as described in Example 1, but employing 3,4,5-trichloroaniline (0.15 g, 0.61 mmol) and the acid chloride (0.15 g, 0.61 mmol), resulting in a 55% yield; m.p. 200-201°C.

Example 72-CHLORO-4-TRIFLUOROMETHYL-5-N-(4-(2',1',3'-  
15 -BENZOTHIADIAZOLE))PYRIMIDINE CARBOXAMIDE

The title compound was prepared as described above in Example 1, but employing 4-amino-2,1,3-benzothiadiazole (0.01 g, 0.07 mmol) and the acid chloride  
20 (0.025 g, 0.10 mmol), resulting in a 60% yield; m.p. 179-180°C.

Example 82-CHLORO-4-TRIFLUOROMETHYL-5-N-(3',5'-DICHLORO-  
25 6'-HYDROXYPHENYL)PYRIMIDINE CARBOXAMIDE

The title compound was prepared as described in Example 1, but employing 3,5-dichloro-6-hydroxyaniline (0.02 g, 0.11 mmol) and the acid chloride (0.04 g, 0.16 mmol), and purified by chromatography (SiO<sub>2</sub>, 1:1 hexanes/EtOAc) to provide the compound in a 10% yield; m.p. 211-213°C.

Example 92-CHLORO-4-TRIFLUOROMETHYL-5-N-[5'-(3'-METHYL-  
30 ISOXAZOLE)]PYRIMIDINE CARBOXAMIDE

The title compound was prepared as described in Example 1, but employing 5-amino-3-methylisoxazole (0.02 g, 0.17 mmol) and the acid chloride (0.03 g,  
35 0.10 mmol), resulting in a 75% yield; m.p. 170-171°C.

Example 102-CHLORO-4-TRIFLUOROMETHYL-5-N-(3'-N-ACYL-  
4'-FLUORO-ANILINE)PYRIMIDINE CARBOXAMIDE

5 A solution of 2-fluoro-5-nitroaniline (1.97 g, 12.60 mmol) and a 1:1 mixture of Ac<sub>2</sub>O/pyridine (20 mL) was stirred for 18 h. The resulting precipitate was filtered and washed with MeOH to provide N-acyl-2-fluoro-5-nitroaniline.

The N-acyl-2-fluoro-5-nitroaniline (0.99 g, 5.00 mmol) was dissolved in EtOH (25 mL), and then 10% Pd/C (0.12 g) was added and the solution stirred under H<sub>2</sub> for 5 h. The suspension was filtered through celite and the filtrate evaporated to dryness. The resulting oil was chromatographed (SiO<sub>2</sub>, 1:3 hexanes/EtOAc) to provide 3-N-acyl-4-fluoro-aniline as a yellow oil. The aniline derivative was then coupled to 2-chloro-4-trifluoromethylpyrimidine-5-carbonyl chloride as described in Example 1 to provide the title compound in a 47% yield; m.p. 126-127°C.

15

Example 112-CHLORO-4-TRIFLUOROMETHYL-5-N-(3'-TRIFLUOROMETHYL-  
5'-CARBOXAMIDEPHENYL) PYRIMIDINE CARBOXAMIDE

To a solution of 3-nitro-5-trifluoromethylbenzoic acid (1.00 g, 4.25 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added oxalyl chloride (1.45 g, 13.8 mmol) followed by DMF (3 drops). An immediate evolution of gas occurred and the reaction was stirred for 18 h. The solvent was removed under reduced pressure, the resulting oil was dissolved in THF (80 mL) and cooled to 0°C. To the cold solution, NH<sub>4</sub>OH (22 mL) in THF (15 mL) was added dropwise and the mixture was stirred 18 h at room temperature. The mixture was concentrated to remove the THF and the resulting precipitate was filtered and dried. The solid was dissolved in EtOH (25 mL) and 10% Pd/C (0.12 g) was added, and the suspension was stirred 15 h under a blanket of H<sub>2</sub>. The reaction was filtered through celite, and the filtrate evaporated to dryness to provide 3-carboxamide-5-trifluoromethylaniline as a yellow oil. This compound was then coupled to 2-chloro-4-trifluoromethylpyrimidine-5-carbonyl chloride as described in Example 1 to provide the title compound in a 55% yield; m.p. 218-219°C.

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Example 122-CHLORO-4-TRIFLUOROMETHYL-5-N-(3'-TRIFLUOROMETHYL-  
5'-ETHOXYCARBONYLPHENYL) PYRIMIDINE CARBOXAMIDE

35

To a solution of 3-nitro-5-trifluoromethylbenzoic acid (0.36 g, 1.53 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added oxalyl chloride (0.58 g, 4.60 mmol) followed by

DMF (3 drops). An immediate evolution of gas occurred and the reaction was stirred for 18 h. The solvent was removed under reduced pressure, the resulting oil was dissolved in THF (80 mL) and cooled to 0°C. To the cooled solution was added EtOH (5 mL) in THF (15 mL) and the mixture was stirred for 18 h at room temperature. The mixture was concentrated to remove the THF and the resulting precipitate was filtered and dried. The solid was dissolved in EtOH (25 mL) and 10% Pd/C (0.12 g) was added and the suspension was stirred for 15 h under a blanket of H<sub>2</sub>. The reaction was filtered through celite and the filtrate evaporated to dryness to provide 3-ethoxycarbonyl-5-trifluoromethylaniline as a yellow oil. This compound was then coupled to 2-chloro-4-trifluoromethyl pyrimidine-5-carbonyl chloride as described above to provide the title compound in a 12% yield; m.p. 67-71°C.

#### Example 13

##### 2-CHLORO-4-TRIFLUOROMETHYL-5-N-(3',5'-DICHLOROPHENYL)- 5-N-(METHYL)PYRIMIDINE CARBOXAMIDE

To a solution of 2-chloro-4-trifluoromethyl-5-N-(3,5-dichlorophenyl)-pyrimidine carboxamide (0.086 g, 0.23 mmol) in DMF (20 mL) was added NaH (0.02 g, 0.53 mmol). The mixture was stirred for 0.3 h at room temperature and then MeI (0.100 mL, 1.61 mmol) was added and stirring continued for 2 h. The solution was acidified with 2N HCl and then extracted with EtOAc (3X). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and the solvent removed under reduced pressure. The resulting oil was chromatographed (SiO<sub>2</sub>, 7:1 hexanes/EtOAc) to provide the title compound (6% yield) as a white solid; m.p. 124-125°C.

#### Example 14

##### 2-CHLORO-4-TRIFLUOROMETHYL-5-N-(3',5'-DICHLOROPHENYL)- 5-N-(BENZYL)PYRIMIDINE CARBOXAMIDE

A mixture of benzaldehyde (1.04 g, 9.40 mmol), 3,5-dichloroaniline (1.71 g, 10.60 mmol), and HOAc (0.20 mL) in MeOH (35 mL) was cooled to 0°C. Then a solution of NaBH<sub>3</sub>CN (28.0 mL, 28.0 mmol, 1.0 M solution in THF) was added dropwise via a syringe pump over 0.25 h. The solution was allowed to stir an additional 0.3 h at 0°C, and then room temperature for 18 h. The excess NaBH<sub>3</sub>CN was quenched with HCl and the solvent was removed under reduced pressure. The resulting oil was dissolved in EtOAc/H<sub>2</sub>O, basified with NaOH, and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and the solvent removed under reduced pressure. The resulting oil was purified by

chromatography (SiO<sub>2</sub>, 15:1 hexanes/EtOAc) to provide N-benzyl-3,5-dichloroaniline as a white solid. This compound was coupled to 2-chloro-4-trifluoromethylpyrimidine-5-carbonyl chloride as described and purified by chromatography (SiO<sub>2</sub>, 9:1 hexanes/EtOAc) to provide the title compound (15% yield) as a white foam; m.p. 102-104°C.

#### Example 15

##### 5-N-[3',5'-BIS(TRIFLUOROMETHYL)PHENYL]- 2,4-DICHLORO-6-METHYLPYRIMIDINE CARBOXAMIDE

5-Carboethoxy-6-methyluracil was prepared as reported in the literature (Lamon, *J. Het. Chem.*, 261, 1969); m.p. 180-182°C. The ethyl ester was then hydrolyzed as described for 2-hydroxy-4-methylpyrimidine-5-carboxylic acid to provide 2,4-dihydroxy-6-methylpyrimidine-5-carboxylic acid in a 95% yield; m.p. >230°C.

The 2,4-dihydroxy-6-methyl pyrimidine-5-carboxylic acid was heated at reflux with POCl<sub>3</sub>. The reaction mixture was concentrated and 2,4-dichloro-6-methylpyrimidine-5-carbonyl chloride was obtained by distillation (b.p. 70-80°C, 1.5 mm/Hg). The 2,4-dichloro-6-methylpyrimidine-5-carbonyl chloride (0.15 g, 0.67 mmol) was immediately reacted with 3,5-bis(trifluoromethyl)aniline (0.15 g, 0.67 mmol) in a similar manner to that described in Example 1 to provide the title compound (0.06 g, 24% - based upon starting 2,4-dihydroxy-6-methylpyrimidine-5-carboxylic acid); m.p. 174-176°C.

#### Example 16

##### 2,4-DICHLOROPYRIMIDINE-5-CARBONYL CHLORIDE

The title compound was prepared as described in the literature (Smith and Christensen, *J. Org. Chem.* 20:829, 1955) starting from 2,4-dihydroxypyrimidine-5-carboxylic acid. The compound was obtained by distillation; b.p. 90-100°C (1.5 mm/Hg) in a yield of 46%; <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ 9.29.

#### Example 17

##### ETHYL UREIDOMETHYLENE ACETOACETATE

A mixture of ethyl acetoacetate (200 g, 1.54 mol), urea (105 g, 1.54 mole) and triethyl orthoformate (228 g, 1.54 mol) was heated at 140°C under N<sub>2</sub> for 22 h. The reaction mixture was cooled and filtered to provide the title compound in a 51% yield (156 g); m.p. 173-174°C.

Example 18

## ETHYL UREIDOMETHYLENE BENZOYLACETATE

The title compound was prepared as described in Example 17, but employing ethyl benzoylacetate (30 g, 156 mmol), resulting in a yield of 21% (12 g);  
5 m.p. 124-126°C.

Example 19

## ETHYL 2-HYDROXY-4-METHYLPYRIMIDINE-5-CARBOXYLATE

A solution of ethyl ureidomethylene acetoacetate (50 g, 250 mmol)  
10 NaOEt (22.1 g, 325 mmol) in EtOH (500 mL) was stirred at room temperature under N<sub>2</sub> for 3 days. The resulting solid was filtered and dried to yield the title compound as a sodium salt in a yield of 88% (45 g); m.p. >220°C (dec.).

Example 20

## 15 ETHYL 2-HYDROXY-4-PHENYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 19, but employing ethyl ureidomethylene benzoyl acetate (12 g, 45 mmol), resulting in a yield of 15% (6 g); m.p. >260°C, (dec.).

20 Example 21

## ETHYL 2-CHLORO-4-METHYLPYRIMIDINE-5-CARBOXYLATE

A solution of ethyl 2-hydroxy-4-methylpyrimidine-5-carboxylate (5 g, 27.5 mmol) and POCl<sub>3</sub> (84 g, 550 mmol) was heated at reflux under N<sub>2</sub> for 1 h. The reaction was cooled and concentrated. The residue was partitioned between CHCl<sub>3</sub> and  
25 H<sub>2</sub>O and the organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to yield the title compound in a yield of 27% (1.5 g); <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ 9.04 (s, 1H), 4.42 (q, 2H), 2.85 (s, 3H), 1.43 (t, 3H).

Example 22

## 30 ETHYL 2-CHLORO-4-PHENYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 21, but employing 2-hydroxy-4-phenylpyrimidine-5-carboxylate (6 g, 25 mmol) to give the title compound (5.5 g, 18%); m.p. 45-47°C.

Example 23

## 2-CHLORO-4-METHYLPYRIMIDINE-5-CARBOXYLIC ACID

A solution of ethyl 2-chloro-4-methylpyrimidine-5-carboxylate (1.0 g, 5 mmol), NaOH (0.24 g, 6 mmol) in H<sub>2</sub>O (30 mL) was stirred at room temperature for 3 h. The solution was acidified with 6N HCl and the resulting solid was filtered and dried to give the title compound (0.67 g 78%), <sup>1</sup>HNMR (DMSO-d<sub>6</sub>) δ 9.01 (s, 1H), 2.75 (s, 3H).

Example 24

## 2-CHLORO-4-PHENYLPYRIMIDINE-5-CARBOXYLIC ACID

The title compound was prepared as described in Example 23, but employing 2-chloro-4-phenylpyrimidine-5-carboxylate (4.5 g, 17 mmol), resulting in a yield of 87% (3.9 g); m.p. 105-110°C.

Example 25

## 2-CHLORO-4-METHYLPYRIMIDINE-5-CARBONYL CHLORIDE

A solution of 2-chloro-4-methylpyrimidine-5-carboxylic acid (0.81 g, 4.70 mmol), oxalyl chloride (0.89 g, 7.05 mmol), DMF (2 drops) in CH<sub>2</sub>Cl<sub>2</sub> (23 mL) was stirred at room temperature under N<sub>2</sub> for 4 h. The solution was concentrated and distilled to give the title compound (0.55 g, 61%); b.p. 90-100°C, 1.3 mm/Hg; <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ d 9.02 (s, 1H), 2.74 (s, 3H).

Example 26

## 2-CHLORO-4-PHENYLPYRIMIDINE-5-CARBONYL CHLORIDE

The compound was prepared as described above in Example 25, but employing 2-chloro-4-phenylpyrimidine-5-carboxylic acid (3.8 g, 14 mmol), resulting in a yield of 53 %; m.p. 42°C.

Example 27

## 2-CHLOROPYRIMIDINE-5-CARBONYLCHLORIDE

The compound was prepared as described in the literature (see, Arukwe, J. Undheim, K. *Acta Chemica Scand.* B40:764, 1986).

Example 28

## ETHYL ETHOXYMETHYLENE-4,4,4-TRIFLUOROACETOACETATE

A solution of 4,4,4-trifluoroacetoacetate (46 g, 0.25 mol) triethyl orthoformate (74 g, 0.50 mol) and  $\text{Ac}_2\text{O}$  (77 g, 0.75 mol) was heated at 120-140°C for 7 h. The mixture was concentrated and distilled to give the title compound in a 98% yield (58.6 g); b.p. 80-90°C, 1.5 mm/Hg.

Example 29

## 2,4-BIS(TRIFLUOROMETHYL)PYRIMIDINE-5-CARBONYL CHLORIDE

A solution of ethyl ethoxymethylene-4,4,4-trifluoroacetoacetate (15 g, 62.5 mmol) and trifluoroacetamide (12.6 g, 112.5 mmol) in EtOH (50 mL) was heated at reflux for 24 h under  $\text{N}_2$ . The reaction mixture was cooled and concentrated. Chromatography ( $\text{SiO}_2$ , 20% EtOAc/hexane) afforded ethyl-2,4-bis(trifluoromethyl)pyrimidine-5-carboxylate as an oil (7.0 g, 39 %),  $^1\text{H}$ NMR ( $\text{CDCl}_3$ )  $\delta$  9.37 (s, 1H), 3.70 (q, 2H), 1.27 (t, 3H).

A solution of ethyl-2,4-bis(trifluoromethyl)pyrimidine-5-carboxylate (5.0 g, 17 mmol) and NaOH (0.72 g, 18 mmol) in EtOH (20 mL) and  $\text{H}_2\text{O}$  (50 mL) was stirred at room temperature for 1 h. The solution was acidified (HCl) and the resulting solid was filtered and dried to give 2,4-bis(trifluoromethyl)-pyrimidine-5-carboxylic acid (1.5 g, 25%), m.p. 59°C,  $^1\text{H}$ NMR ( $\text{DMSO}-d_6$ )  $\delta$  9.62 (s, 1H).

The desired acid chloride was obtained from 2,4-bis(trifluoromethyl)-pyrimidine-5-carboxylic acid in a manner similar to that described in Example 25 in a yield of 44%; b.p. 105°C (1.5 mm/Hg);  $^1\text{H}$ NMR ( $\text{CDCl}_3$ )  $\delta$  9.12 (s, 1H).

Example 30

## 2-CHLORO-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLIC ACID

A solution of 2-chloro-4-trifluoromethylpyrimidine-5-carbonyl chloride (2.1 g, 8.6 mmol) in  $\text{H}_2\text{O}$  (10 mL) was stirred at 0°C under  $\text{N}_2$  for 0.5 h. The resulting solid was filtered and dried to give the title compound (1.91 g, 98% yield); m.p. 232-234°C (dec.).

Example 31

## 2-CYANO-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBONYLCHLORIDE

To a solution of 2-chloro-4-trifluoromethylpyrimidine-5-carboxylic acid (2.80 g, 12.4 mmol) in THF (50 mL) at 0°C. was added  $\text{Me}_3\text{N}$  (bubbled for 5 minutes). The reaction was kept at 0°C for 0.25 h and the resulting solid was filtered to provide 2-



trimethylammonium chloride-4-trifluoromethylpyrimidine-5-carboxylic acid (3.40 g, 97% yield); m.p. 120-121°C (dec.).

A solution of 2-trimethylammonium chloride-4-trifluoromethylpyrimidine-5-carboxylic acid (3.62 g, 12.7 mmol) and KCN (0.99 g, 15.2 mmol) in DMF (36.5 mL) and H<sub>2</sub>O (18.3 mL) was stirred at room temperature under N<sub>2</sub> for 0.25 h. The reaction mixture was concentrated and dissolved in EtOAc (400 mL). The EtOAc layer was washed with H<sub>2</sub>O (4 X 100 mL), brine (100 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). The EtOAc layer was filtered and concentrated to yield 2-cyano-4-trifluoromethylpyrimidine-5-carboxylic acid (2.03 g, 74% yield); m.p. 148-149°C (dec.).

A solution of 2-cyano-4-trifluoromethylpyrimidine-5-carboxylic acid (2.0 g, 9.2 mmol), oxalyl chloride (1.4 g, 11 mmol) and DMF (4 drops) in CH<sub>2</sub>Cl<sub>2</sub> (46 mL) was stirred at room temperature under N<sub>2</sub> for 0.75 h. The reaction was concentrated and distilled (b.p. 100°C, 1.5 mm/Hg) to give the title compound (1.8 g, 82% yield); <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ 9.49 (s, 1H).

#### Example 32

##### 2-PHENYLPYRIMIDINE-5-CARBONYL CHLORIDE

A solution of ethyl 3-N,N-dimethylamino-2-formylacrylate (4.0 g, 23 mmol) (Arnold, *Coll. Czech. Chem. Commun.* 26:3051, 1961), benzamidine hydrochloride (4.0 g, 26 mmol) and sodium (0.65 g, 28 mmol) in EtOH (40 mL) was heated at reflux for 1 h. The solution was filtered and concentrated and the residue partitioned between EtOAc and dilute HCl (10%). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to give ethyl 2-phenylpyrimidine-5-carboxylate (4.0 g, 75% yield); m.p. >220°C (dec.).

The corresponding 2-phenylpyrimidine-5-carboxylic acid was prepared in a yield of 80% (0.35 g) starting from ethyl 2-phenylpyrimidine-5-carboxylate in a similar manner to that described in Example 23; m.p. > 220°C (dec.).

The title compound was prepared in a quantitative yield from 2-phenylpyrimidine-5-carboxylic acid in a similar manner to that described in Example 25; m.p. 135°C.

#### Example 33

##### ETHYL 2-TRIFLUOROMETHYL-4-HYDROXYPYRIMIDINE-5-CARBOXYLATE

A solution of diethyl ethoxymethylenemalonate (35.0 g, 162 mmol), trifluoroacetamidine (18 g, 162 mmol) and NaOEt (11.0 g, 162 mmol) in EtOH (200 mL) was heated at reflux for 6 h. The reaction mixture was concentrated and H<sub>2</sub>O (48

mL) was added. The resulting solid was filtered, washed with Et<sub>2</sub>O (300 mL) and H<sub>2</sub>O (200 mL), and dried to give the title compound (21 g, 50% yield); m.p. >220°C (dec.); <sup>1</sup>HNMR (DMSO-d<sub>6</sub>) δ 8.38, 4.16 (q, 2H), 1.25 (q, 3H).

5

#### Example 34

##### 2-TRIFLUOROMETHYL-4-CHLOROPYRIMIDINE-5-CARBONYL CHLORIDE

A solution of ethyl 2-trifluoromethyl-4-hydroxypyrimidine-5-carboxylate (5.00 g, 19.4 mmol) and NaOH (0.93 g, 23.3 mmol) in H<sub>2</sub>O (20 mL) was stirred at 60°C for 15 h. The reaction was acidified (conc. HCl) and concentrated until a solid began to form. The solid was filtered and dried to give 2-trifluoromethyl-4-hydroxypyrimidine-5-carboxylic acid (2.1 g, 53% yield); <sup>1</sup>HNMR (DMSO-d<sub>6</sub>) δ 8.83 (s, 1H).

A solution of 2-trifluoromethyl-4-hydroxypyrimidine-5-carboxylic acid (2.0 g, 10.4 mmol), POCl<sub>3</sub> (32 g, 212 mmol) and SOCl<sub>2</sub> (25 g, 212 mmol) was heated at reflux for 4 days. The reaction was concentrated and distilled (b.p. 90-95°C, 1.5 mm/Hg) to provide the title compound (2.1 g, 81% yield), <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ 9.45 (s, 1H).

#### Example 35

##### 2-CHLORO-4-PENTAFLUOROETHYLPYRIMIDINE-5-CARBONYL CHLORIDE

A solution of ethyl 2-hydroxy-4-pentafluoroethylpyrimidine-5-carboxylate (4.0 g, 13 mmol) and NaOH (1.60 g, 39 mmol) in EtOH (20 mL) and H<sub>2</sub>O (45 mL) was heated at reflux for 1 h. The solution was cooled and acidified (conc. HCl). The resulting solid was filtered and dried to provide 2-hydroxy-4-pentafluoroethylpyrimidine-5-carboxylic acid (3.3 g, 98% yield); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 9.90 (bs, 1H), 8.43 (s, 1H).

A solution of 2-hydroxy-4-pentafluoroethylpyrimidine-5-carboxylic acid (3.33 g, 12.9 mmol) in SOCl<sub>2</sub> (27.7 g, 233 mmol) was heated at reflux for 0.5 h. Then POCl<sub>3</sub> (35.6 g, 233 mmol) was added to the reaction mixture and heating continued for 36 h. The reaction mixture was concentrated and distilled (b.p. 80-85°C, 1 mm/Hg) to give the title compound (1.2 g, 35% yield). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 9.18 (s, 1H).

#### Example 36

##### 4-TRIFLUOROMETHYL-5-N-

##### (3',5'-DICHLOROPHENYL)PYRIMIDINE CARBOXAMIDE

A solution of 2-chloro-4-trifluoromethyl-5-N-(3,5-dichlorophenyl)pyrimidine carboxamide (0.10 g, 0.27 mmol), Mg<sub>2</sub>O (0.024 g, 0.59

mmol) and 5% Pd/C (0.01 g) in EtOH (1.8 mL) and water (0.9 mL) was stirred at room temperature under a blanket of H<sub>2</sub> for 2.5 h. The reaction mixture was concentrated and chromatographed (SiO<sub>2</sub>, 9% EtOAc/hexane) to yield the title compound (0.05 g, 53% yield); m.p. 189-190°C.

5

#### Example 37

##### 2-DIMETHYLAMINO-4-TRIFLUOROMETHYL-

##### 5-N-(3',5'-DICHLOROPHENYL) PYRIMIDINE CARBOXAMIDE

A solution of 2-chloro-4-trifluoromethyl-5-N-(3,5-dichlorophenyl)pyrimidine carboxamide (0.13 g, 0.36 mmol) and dimethyl amine (0.10 g, 2.20 mmol) in MeOH was stirred at room temperature for 3 h. The reaction mixture was concentrated and chromatographed (SiO<sub>2</sub>, 5% EtOAc/hexane) to afford the title compound (0.022 g, 16% yield); m.p. 163-164°C.

15

#### Example 38

##### 2-TRIETHYLAMMONIUM CHLORIDE-4-TRIFLUOROMETHYL-

##### 5-N-(3',5'-DICHLOROPHENYL) PYRIMIDINE CARBOXAMIDE

A solution of 2-chloro-4-trifluoromethyl-5-N-(3',5'-dichlorophenyl)pyrimidine carboxamide (0.10 g, 0.27 mmol) and triethylamine (0.027 g, 0.27 mmol) in dry THF was stirred for 24 h. The solid was filtered, washed with Et<sub>2</sub>O, and dried to afford the title compound (0.031 g, 24% yield); m.p. 158-159°C.

#### Example 39

##### 2-CHLORO-4-METHYL-5-N-[3',5'-BIS(TRIFLUORO-

##### METHYL)PHENYL]PYRIMIDINE CARBOXAMIDE

A solution of 2-chloro-4-methylpyrimidine-5-carbonyl chloride (0.10 g, 0.53 mmol), 3,5-bis(trifluoromethyl)aniline (0.12 g, 0.53 mmol) and Amberlyst A-21 resin (0.10g) in EtOAc (5.3 mL) was stirred at room temperature for 1 h. The solution was filtered, concentrated and chromatographed (SiO<sub>2</sub>, 10% EtOAc/hexane) to afford the title compound (0.17 g, 84% yield); m.p. 156-157°C.

#### Example 40

##### 2,4-DICHLORO-5-N-[3',5'-BIS(TRIFLUORO-

##### METHYL)BENZYL]PYRIMIDINE-5-CARBOXAMIDE

The title compound was prepared as described in Example 1, but employing 2,4-dichloropyrimidine-5-carbonylchloride (0.10 g, 0.40 mmol) and 3,5-

35

bistrifluoromethylbenzylamine (0.10 g, 0.45 mmol) to give the compound in a 61% yield (0.12 g); m.p. 144-145°C.

#### Example 41

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2,4-DICHLORO-5-N-[3',5'-BIS(TRIFLUORO-  
METHYL)PHENYL]PYRIMIDINE-5-CARBOXAMIDE

The title compound was prepared as described in Example 1, but employing 2,4-dichloropyrimidine-5-carbonyl chloride to give the compound in a 97% yield (0.28 g); m.p. 104-105°C.

10

#### Example 42

2-CYANO-4-TRIFLUOROMETHYL-5-N-[3',5'-BIS(TRIFLUORO-  
METHYL)PHENYL]PYRIMIDINE CARBOXAMIDE

15 The title compound was prepared as described in Example 1, but employing 2-cyano-4-trifluoromethylpyrimidine-5-carbonyl chloride (0.11 g, 0.46 mmol) to give the compound in a 96% yield (0.19 g); m.p. 146-147°C.

#### Example 43

20

2-CHLORO-4-PHENYL-5-N-[3',5'-BIS(TRIFLUORO-  
METHYL)PHENYL]PYRIMIDINE CARBOXAMIDE

A solution of 2-chloro-4-phenylpyrimidine-5-carbonyl chloride (0.10 g, 0.40 mmol), 3,5-bis(trifluoromethyl) aniline (0.08 g, 0.40 mmol) and Et<sub>3</sub>N (0.04 g, 0.40 mmol) in EtOAc was stirred at room temperature for 2 h. The solution was concentrated and chromatographed (SiO<sub>2</sub>, 5% EtOH/CHCl<sub>3</sub>) to afford the title  
25 compound (0.08 g, 45% yield); m.p. 154°C.

#### Example 44

2-HYDRAZINO-4-TRIFLUOROMETHYL-5-N-  
(3',5'-DICHLOROPHENYL)PYRIMIDINE-5-CARBOXAMIDE

30

A solution of 2-chloro-4-trifluoromethyl-5-N-(3',5'-dichlorophenyl)pyrimidine carboxamide (0.10 g, 0.27 mmol) and hydrazine (0.009 g, 0.54 mmol) in THF was stirred under N<sub>2</sub> at room temperature for 14 h. The solution was filtered, concentrated and chromatographed (SiO<sub>2</sub>, 20% EtOAc/hexane) to afford the title compound (0.08 g, 79% yield), <sup>1</sup>HNMR (acetone-d<sub>6</sub>) δ 10.08 (bs, 1H), 9.64 (bs, 1H), 8.89 (s, 1H), 7.80 (s, 2H), 7.24 (s, 1H), 2.79 (bs, 2H).  
35

Example 452-[N-(1-AMINOCITRACONAMIDE)]-4-TRIFLUOROMETHYL-  
5-[N-(3',5'-DICHLOROPHENYL)]-PYRIMIDINE-5-CARBOXAMIDE

5 A solution of 2-hydrazino-4-trifluoromethyl-5-[N-(3',5'-dichlorophenyl)pyrimidine carboxamide (0.08 g, 0.21 mmol) and citraconic anhydride (0.024 g, 0.21 mmol) in  $\text{CHCl}_3$  (2.1 mL) was heated at reflux under  $\text{N}_2$  for 24 h. The solution was concentrated and chromatographed ( $\text{SiO}_2$ , 33% EtOAc/hexane) to afford the title compound (0.06 g, 62% yield); m.p. 182-183°C.

Example 462-PHENYLAMINO-4-TRIFLUOROMETHYL-  
5-N-(3',5'-DICHLOROPHENYL)-PYRIMIDINE-5-CARBOXAMIDE

10 A solution of 2-chloro-4-trifluoromethyl-5-N-(3',5'-dichlorophenyl)pyrimidine carboxamide (0.10 g, 0.27 mmol) and aniline (0.06 g, 0.59 mmol) in dry THF (2.7 mL) was stirred at room temperature under  $\text{N}_2$  for 18 h. The reaction mixture was filtered, concentrated and chromatographed ( $\text{SiO}_2$ , 50%  $\text{CHCl}_3$ /hexane) to afford the title compound (0.10 g, 91% yield); m.p. 228-229°C.

Example 47

## 20 METHYL 5-CHLORO-6-METHYL-2-PYRAZINE CARBOXYLATE.

To a solution of methyl 4,5-dihydro-6-methyl-5-oxo-2-pyrazine carboxylate (M. Mano, T. Seo, K. Imai, *Chem. Pharm. Bull* 10:3057-3063, 1980) in DMF (20 mL) was added  $\text{POCl}_3$  (20 mL). The reaction was refluxed for 0.5 h and then poured into ice. The aqueous layer was extracted with  $\text{CHCl}_3$ , dried ( $\text{MgSO}_4$ ) and  
25 concentrated. The residue was chromatographed ( $\text{SiO}_2$ ,  $\text{CHCl}_3$ ) to provide the title compound (2.34 g, 52% yield); m.p. 49-50°C.

Example 48

## 5-CHLORO-6-METHYL-2-PYRAZINECARBOXYLIC ACID

30 A mixture of methyl 5-chloro-6-methyl-2-pyrazine carboxylate (0.16 g, 0.86 mmol),  $\text{K}_2\text{CO}_3$  (0.31 g, 2.18 mmol) and  $\text{H}_2\text{O}$  was stirred for 2 h at room temperature. The reaction was filtered and acidified (20% HCl), and the resulting solid collected to provide the title compound (0.057 g, 39% yield); m.p. 116-117°C.

Example 49**2-CHLORO-5-N-(BISTRIFLUOROMETHYL ANILINE)  
PYRAZINE CARBOXAMIDE**

The title compound was prepared in a yield of 51% (0.08 g) using the  
5 same procedure as outlined in Example 1, except substituting 2-chloro-5-pyrazine  
carbonyl chloride (0.1 g, 0.57 mmol.) in place of the pyrimidine carbonyl chloride; m.p.  
101-102°C.

Example 50

10 **2-TRIMETHYLAMMONIUM CHLORIDE-4-TRIFLUOROMETHYL-  
5-PYRIMIDINE CARBOXYLIC ACID**

A solution of 2-chloro-4-trifluoromethylpyrimidine-5-carboxylic acid (6.0  
g, 27 mmol) and excess trimethyl amine in THF (60 mL) was stirred for 5 min. The  
solid was filtered and dried to yield 97% (7.1 g) of the title compound; <sup>1</sup>H NMR  
15 (DMSO-d<sub>6</sub>) δ 9.19 (s, 1H), 2.72 (s, 9H).

Example 51

**2-FLUORO-4-TRIFLUOROMETHYL-  
5-PYRIMIDINE CARBOXYLIC ACID**

20 A mixture of 2-trimethylammonium chloride-4-trifluoromethyl-5-  
pyrimidine carboxylic acid (4.3 g, 15 mmol), KF (1.8 g, 30 mmol), DMF (40 mL) and  
H<sub>2</sub>O (20 mL) was stirred for 0.5h. The mixture was concentrated, acidified and  
extracted with Et<sub>2</sub>O. The Et<sub>2</sub>O layer was concentrated to yield 47% (1.6 g) of the title  
compound; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 9.41 (s, 1H).

25

Example 52**2-FLUORO-4-TRIFLUOROMETHYL-  
5-PYRIMIDINE CARBONYL CHLORIDE**

The title compound was prepared as described in Example 25, but  
30 employing a solution of 2-fluoro-4-trifluoromethylpyrimidine-5-carboxylic acid (1.5 g,  
7.1 mmol) and oxalyl chloride (1.0 g, 8 mmol), DMF (2 drops) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL)  
resulted in a 75% yield (1.2 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.42 (s, 1H).

Example 53

2-FLUORO-4-TRIFLUOROMETHYL-5-N-[3',5'-BIS(TRIFLUOROMETHYL)PHENYL]  
PYRIMIDINE CARBOXAMIDE

The title compound was prepared as described in Example 1, but  
5 employing a solution of 2-fluoro-4-trifluoromethylpyrimidine-5-carbonyl chloride (0.05 g, 0.22 mmol) and 3,5-bis(trifluoromethyl)aniline (45 mg, 0.2 mmol) in EtOAc (2 mL) resulted in a 22% yield (0.02 g); m.p. 133-135°C.

Example 54

10 2-CHLORO-4-TRIFLUOROMETHYL-  
5-PYRIMIDINE CARBONYL CHLORIDE

The title compound was prepared as described in Example 25, but  
employing a solution of 2-chloro-4-trifluoromethylpyrimidine-5-carboxylic acid (1.5 g,  
7.1 mmol) and oxalyl chloride (1.0 g, 8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) resulted in a 70%  
15 yield (1.1g); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.31 (s, 1H).

Example 55

SYNTHESIS OF REPRESENTATIVE COMPOUNDS  
BY COMBINATORIAL CHEMISTRY TECHNIQUES

20 This example illustrates the synthesis of a representative class of compounds of this invention by combinatorial chemistry. It should be understood that, while a specific class of compounds are illustrated in this example, the following procedure may be employed to synthesize other compounds of this invention.

Into wells 2-11 of a 96 well 1 mL plate (rows 1 and 12 left open as  
25 controls) was added 5 mg of Amberlyst 21 resin, 0.2 mL of EtOAc and 22.4 μmol of 80 different amine derivatives. Then to each well was added 25.0 μmol of the appropriate 5-carbonyl chloride (for example 2-chloro-4-trifluoromethylpyrimidine-5-carbonyl chloride). The 96 well plate was sonicated for 0.3 h and 50 μL of H<sub>2</sub>O was added to each well. The plate was sonicated for an additional 0.25 h, and the EtOAc layer from  
30 each well was removed and concentrated to provide 80 individual compounds. Thin-layer chromatography, HPLC and GC/MS analysis indicated that the desired compounds had been produced at >90% purity. This approach can be used to generate large numbers of derivatives for each substituted pyrimidine prepared, and can be used to routinely prepare >160 derivatives for each of the different 5-carbonyl pyrimidines.

Example 56INHIBITION OF THE ACTIVATION OF NF $\kappa$ B AND AP-1A. NF $\kappa$ B ASSAY

5 Stable human Jurkat T-cells containing an NF $\kappa$ B binding site (from the MHC promoter) fused to a minimal SV-40 promoter driving luciferase expression were used in this experiment. Cells were split to  $3 \times 10^5$  cells/mL every 2-3 days (cell concentration should not exceed  $1 \times 10^6$  cells/mL to keep the cells proliferating in log phase). These cells were counted, resuspended in fresh medium containing 10% Serum-  
10 Plus at a density of  $1 \times 10^6$  cells/mL and plated in 96 well round bottom plates (200  $\mu$ L per well) 18 hours prior to starting the experiment.

Compounds of this invention, dissolved in dimethyl sulfoxide (3.3, 0.33 and 0.03  $\mu$ g/mL), were then added to the 96 well plates containing the cells and the plates are incubated for 0.5 h at 37°C. Then 50 ng/mL of phorbol 12-myristate-13-  
15 acetate (PMA) and 1  $\mu$ g/mL of phytohemagglutinin (PHA) was added to each well and the cells were incubated for an additional 5 h at 37°C. The plates were centrifuged at 2200 RPM for 3 minutes at room temperature and then the medium was removed. To each well was added 60  $\mu$ L of cell lysis buffer and the plates were left at room temperature for 0.25 h. Then 40  $\mu$ L of each cell extract was transferred to a black 96  
20 well plate and 50  $\mu$ L of luciferase substrate buffer was added. Luminescence was immediately measured using a Packard TopCount.

## B. AP-1 ASSAY

For AP-1, the assay was run as described above for NF $\kappa$ B except stable  
25 Jurkat T-cells were used that contained a collagenase promoter driving luciferase expression. In addition, the concentration of PMA used was 5 ng/mL.

## C. RESULTS

The results of the above assays for a representative compound of this  
30 invention, 2-chloro-4-trifluoromethyl-5-N-(3',5'-bistrifluoromethylphenyl)pyrimidine carboxamide, as percent inhibition versus control are presented in Figure 3. This figure also indicates activity of  $\beta$ -actin which was employed in these assays as a control cell line indicating effects on transcription. The lack of  $\beta$ -actin activity evidences selectivity of the test compounds for the transcription factors AP-1 and NF $\kappa$ B.

35 Expressed as IC<sub>50</sub>'s, the results of these assays on additional test compounds are summarized in Table 2 below.



Table 2

<u>Test Compound</u> <u>(Example #)</u>	<u>NFκB/AP-1</u> <u>IC<sub>50</sub> (μM)</u>
1	0.03
2	0.75
6	0.8
8	6.0
10	1.0
11	5.0
12	0.4
13	5.0
15	0.8
39	0.075
41	0.6
42	>10
43	0.5
45	2.0

Based on the results of this experiment, representative compounds of this invention were found to be effective at inhibiting the activation of transcription factors (*i.e.*, NFκB and AP-1) involved in gene transcription, and therefore have utility as, for example, immunosuppressive agents.

Example 57

10

## INHIBITION OF CYTOKINES

To determine the effects of compounds on PMA/PHA-induced cytokine production, supernatants from either the NFκB (for IL-8) and AP-1 (for IL-2) reporter gene assays of Example 56 were collected and saved. Cytokine levels in the supernatants (25-50 μL aliquots) were determined by ELISA. The results of this experiment for a representative compound of this invention, 2-chloro-4-trifluoromethyl-5-N-(3',5'-bistrifluoromethylphenyl)pyrimidine carboxamide, is presented in Figure 4 (expressed as percent inhibition versus control).

Example 58

20

*IN VIVO* ACTIVITY OF REPRESENTATIVE COMPOUND

The murine popliteal lymph node (PLN) assay is a graft vs. host model that predicts activity of compounds in blocking human transplant rejection. The delayed-type hypersensitivity response to oxazolone is a standard contact sensitivity model. Both

of these models are used routinely to evaluate compounds that are used clinically. For example, cyclosporin and cyclophosphamide are active in these models and are used clinically (Morris et al., *Transplantation Proceedings* 22(Suppl. 1):110-112, 1990).

5 A. POPLITEAL LYMPH NODE MODEL

Spleens were removed from donor BALB/c mice and splenocytes were isolated then irradiated (3,000 rads) to prevent donor cell proliferation. After washing and adjusting cell density,  $2.5 \times 10^6$  cells were injected subcutaneously into the left hind footpad of C3H mice. On day 4, the mice were sacrificed and left popliteal lymph nodes  
10 (PLNs) were weighed.

The compound of Example 1, 2-chloro-4-trifluoromethyl-5-N-(3',5'-bistrifluoromethylphenyl)pyrimidine carboxamide, was administered once daily by intraperitoneal injection beginning one day before footpad injection (day 0) through day 4. The compound was suspended, immediately prior to use, at a concentration of 5  
15 mg/mL in 0.25% methyl cellulose (Sigma) using a glass-teflon homogenizer. For doses of 10, 20 and 30 mg/kg, appropriate dilutions of the stock solution were made so that 0.1 mL/10 g body weight was administered by intraperitoneal injection.

The results of this experiment, presented in Figure 5, demonstrate that a representative compound of this invention caused a dose-dependent suppression of  
20 alloantigen-induced PLN proliferation. The lowest dose of this compound, 10 mg/kg, caused a 52% inhibition of proliferation whereas cyclosporin A, at 12 mg/kg, caused a 35% inhibition.

B. DELAYED TYPE HYPERSENSITIVITY STUDY

25 On day 0, oxazolone (100  $\mu$ L of a 3% solution) was applied to the shaved abdomen of mice. On day 7, a challenge application of oxazolone was applied (10  $\mu$ L) around the right ear. The compound of Example 1, 2-chloro-4-trifluoromethyl-5-N-(3,5-bistrifluoromethylphenyl)pyrimidine carboxamide, was administered from days -2 to 7 by intraperitoneal injection. It was prepared immediately prior to use by  
30 suspending it in 0.25% methyl cellulose (Sigma) using a glass-teflon homogenizer. For each dose, 0.1 mL/10 g body weight of the suspension was administered. The compound was prepared at the highest concentration for that study and appropriate dilutions of the stock solution were made so that 0.1 mL/10 g body weight was administered. Twenty four hours later, the difference in right vs. left ear thickness was  
35 measured. The results of this experiment are presented in Table 3 below.

Table 3Effect on the DTH Response to Oxazolone

Compound	Dose (mg/kg)	Right-Left Ear (mean $\pm$ SEM)	P Value (vs. vehicle)
Vehicle only	---	0.30 $\pm$ 0.02	---
Test Cpd.	10 (i.p.)	0.27 $\pm$ 0.01	0.163
Test Cpd.	30 (i.p.)	0.13 $\pm$ 0.02	<0.001*
Cyclophosphamide	50 (i.p.)	0.08 $\pm$ 0.01	<0.001

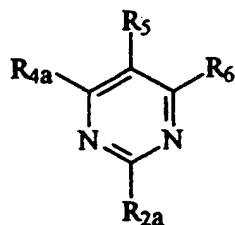
\*One animal died during study

5                   The test compound (30 mg/kg i.p.) and cyclophosphamide (50 mg/kg i.p.) significantly attenuated the delayed-type response to oxazolone by 56% and 73%, respectively.

10                   It will be appreciated that, although specific embodiments of this invention have been described herein for purpose of illustration, various modifications may be made without departing from the spirit and scope of the invention.

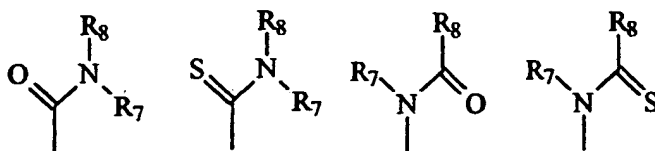
### Claims

1. A compound having the structure:



including pharmaceutically acceptable salts thereof, wherein

R<sub>5</sub> is selected from the following chemical moieties:



R<sub>7</sub> is selected from hydrogen, -CH<sub>3</sub>, and -CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>;

R<sub>8</sub> is selected from hydrogen and an unsubstituted or substituted C<sub>1-8</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub> aralkyl, C<sub>3-12</sub>heterocycle and a C<sub>4-20</sub> heterocyclealkyl;

R<sub>2a</sub> is selected from halogen, an unsubstituted or substituted C<sub>1-8</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl, C<sub>3-12</sub>heterocycle or C<sub>4-20</sub>heterocyclealkyl, -CN, -OR, -NRR and -NRNCOR;

R<sub>4a</sub> is selected from hydrogen, halogen, an unsubstituted or substituted C<sub>1-8</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl, C<sub>3-12</sub>heterocycle or C<sub>4-20</sub>heterocyclealkyl, -CN, -OR, -NRR and -NRNCOR; and

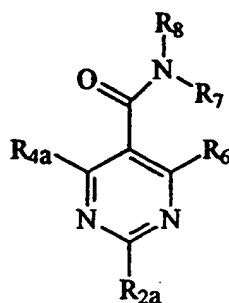
R<sub>6</sub> is selected from hydrogen, halogen and an unsubstituted or substituted C<sub>1-8</sub>alkyl;

and wherein each occurrence of R is independently selected from an unsubstituted or substituted C<sub>1-8</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl, C<sub>3-12</sub>heterocycle or C<sub>4-16</sub>heterocyclealkyl;

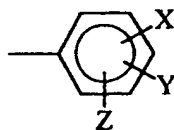
with the provisos that: (a) when R<sub>5</sub> is -CONR<sub>7</sub>R<sub>8</sub>, (i) R<sub>7</sub> and R<sub>8</sub> are not both hydrogen, (ii) R<sub>2a</sub> is not selected from -N(CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -OR, and an unsubstituted, straight chain or branched, non-cyclic, saturated C<sub>1-3</sub>alkyl, -N(CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub> and -OR, (iii) when R<sub>2a</sub> is -Cl and R<sub>6</sub> is -H, R<sub>4a</sub> is not selected from -CF<sub>3</sub>, -Cl, -CH<sub>3</sub> and -C(CH<sub>3</sub>)<sub>3</sub>, (iv) when R<sub>2a</sub> is -Cl and both R<sub>4a</sub> and R<sub>6</sub> are -H, R<sub>8</sub> is not -CH(CN)C<sub>6</sub>H<sub>5</sub>, and (v) when R<sub>2a</sub> is -Cl and R<sub>4a</sub> is -Cl, R<sub>6</sub> is not selected from -Cl and -CH<sub>2</sub>Cl; and (b) when R<sub>5</sub> is -N(R<sub>7</sub>)C(=O)R<sub>8</sub>,

(i)  $R_{2a}$  is not selected from  $-CH_3$ ,  $-OCH_3$  and  $-N(CH_3)_2$ , and (ii)  $R_8$  is not selected from  $-H$  and  $-CH_3$ .

2. The compound of claim 1 having the structure:



3. The compound of claim 2 wherein  $R_{4a}$  is selected from  $-CF_3$ ,  $-Cl$ ,  $-F$ ,  $-CH_3$  and  $-H$ .
4. The compound of claim 2 wherein  $R_{2a}$  is selected from  $-Cl$ ,  $-OCH_3$ ,  $-H$ ,  $-N(CH_3)_2$ ,  $-CF_3$ ,  $-CN$ ,  $-NHNH_2$  and  $-NHC_6H_5$ .
5. The compound of claim 2 wherein  $R_6$  is selected from  $-H$ ,  $-CF_3$ ,  $-CH_3$  and  $-Cl$ .
6. The compound of claim 2 wherein  $R_7$  is selected from  $-H$  and  $-CH_3$ .
7. The compound of claim 2 wherein  $R_8$  is



wherein X, Y and Z are the same or different, and independently selected from hydrogen,  $-OH$ ,  $-R$ ,  $-OR$ ,  $-COOH$ ,  $-COOR$ ,  $-COR$ ,  $-CONH_2$ ,  $-NH_2$ ,  $-NHR$ ,  $-NRR$ ,  $-SH$ ,  $-SR$ ,  $-SOOR$ ,  $-SO_3R$  and  $-SOR$ .

8. The compound of claim 2 wherein  $R_{4a}$  is  $-CF_3$  and  $R_{2a}$  is  $-Cl$ .
9. The compound of claim 2 wherein  $R_{4a}$  is  $-CF_3$ .

10. The compound of claim 9 wherein the compound is selected from 2-fluoro-4-trifluoromethyl-5-N-(3',5'-bistrifluoromethyl)pyrimidine carboxamide, 5-(3',5'-bis(trifluoromethyl)phenacyl)-2-methoxy-4-trifluoromethylpyrimidine; 4-trifluoromethyl-5-N-(3',5'-dichlorophenyl)pyrimidine carboxamide; 2-dimethylamino-4-trifluoromethyl-5-N-(3',5'-dichlorophenyl)pyrimidine carboxamide; 2-triethylammonium chloride-4-trifluoromethyl-5-N-(3',5'-dichlorophenyl)pyrimidine carboxamide; 2-cyano-4-trifluoromethyl-5-N-[3',5'-(bistrifluoromethyl)phenyl]pyrimidine carboxamide; 2-hydrazino-4-trifluoromethyl-5-[N-(3',5'-dichlorophenyl)pyrimidine-5-carboxamide]; 2-[N-(1-aminocitraconamide)]-4-trifluoromethyl-5-[N-(3',5'-dichlorophenyl)pyrimidine-5-carboxamide]; and 2-aminophenyl-4-trifluoromethyl-N-(3',5'-dichlorophenyl)pyrimidine-5-carboxamide.

11. The compound of claim 2 wherein  $R_2$  is -Cl.

12. The compound of claim 11 wherein the compound selected from 5-N-[3',5'-bis(trifluoromethyl)phenyl]-2,4-dichloro-6-methyl-pyrimidine carboxamide; 2-chloro-4-methyl-5-N-[3',5'-(bistrifluoromethyl)phenyl]pyrimidine carboxamide; 2,4-dichloro-5-N-[3',5'-bis(trifluoromethyl)benzyl]pyrimidine-5-carboxamide; and 2-chloro-4-phenyl-5-N-[3',5'-(bistrifluoromethyl)phenyl]pyrimidine carboxamide.

13. The compound of claim 2 wherein  $R_8$  is a 3,5-disubstituted phenyl moiety, wherein both substituents are electron withdrawing groups.

14. The compound of claim 13 wherein both substituents are  $-CF_3$ .

15. The compound of claim 13 wherein at least one of the substituents is  $-CF_3$ .

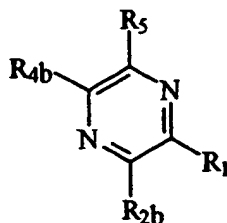
16. The compound of claim 2 wherein  $R_4$  is selected from -H,  $-CH_3$ ,  $-CF_3$ ,  $-CF_2CF_3$ ,  $-C_6H_5$  and  $-CH_2C_6H_5$ .

17. The compound of claim 2 wherein  $R_2$  is selected from -Cl, -F, -CN and  $-CF_3$ .

18. The compound of claim 2 wherein  $R_2$  is selected from -Cl and -F.

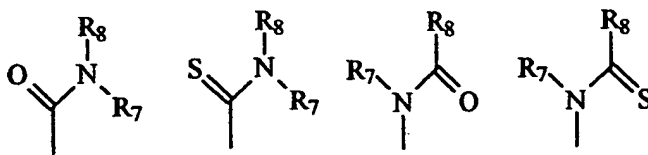
19. The compound of claim 2 wherein  $R_6$  is -H.

20. A compound having the structure:



including pharmaceutically acceptable salts thereof, wherein

$R_5$  is selected from the following chemical moieties:



$R_7$  is selected from hydrogen,  $-CH_3$ , and  $-CH_2C_6H_5$ ;

$R_8$  is selected from hydrogen and an unsubstituted or substituted  $C_{1-8}$ alkyl,  $C_{6-12}$ aryl,  $C_{7-12}$  aralkyl,  $C_{3-12}$ heterocycle and a  $C_{4-20}$  heterocyclealkyl;

$R_{2b}$  is halogen;

$R_{4b}$  is selected from hydrogen, halogen,  $-CN$ , and an unsubstituted or substituted  $C_{1-8}$ alkyl,  $C_{6-12}$ aryl,  $C_{7-12}$ aralkyl,  $C_{3-12}$ heterocycle or  $C_{4-20}$ heterocyclealkyl; and

$R_1$  is selected from hydrogen,  $-CH_3$ ,  $-CF_3$  and  $-CH_2CH_3$ ;

and wherein each occurrence of R is independently selected from an unsubstituted or substituted  $C_{1-8}$ alkyl,  $C_{6-12}$ aryl,  $C_{7-12}$ aralkyl,  $C_{3-12}$ heterocycle or  $C_{4-16}$ heterocyclealkyl;

with the proviso that when  $R_5$  is  $-CONR_7R_8$  and  $R_{2b}$  is  $-Cl$ ,  $R_{4b}$  and  $R_1$  are not both hydrogen.

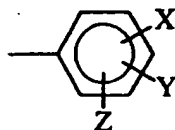
21. The compound of claim 20 wherein  $R_{4b}$  is an unsubstituted  $C_{1-8}$ alkyl.

22. The compound of claim 20 wherein  $R_{2b}$  is selected from  $-Cl$  and  $-F$ .

23. The compound of claim 20 wherein  $R_1$  is selected from  $-H$  and  $-CH_3$ .

24. The compound of claim 20 wherein  $R_7$  is selected from  $-H$  and  $-CH_3$ .

25. The compound of claim 20 wherein  $R_8$  is



wherein X, Y and Z are the same or different, and independently selected from hydrogen, -OH, -R, -OR, -COOH, -COOR, -COR, -CONH<sub>2</sub>, -NH<sub>2</sub>, -NHR, -NRR, -SH, -SR, -SOOR, -SO<sub>3</sub>R and -SOR.

26. The compound of claim 20 wherein  $R_{4b}$  is -CF<sub>3</sub> and  $R_{2b}$  is -Cl.
27. The compound of claim 20 wherein  $R_{4b}$  is -CF<sub>3</sub>.
28. The compound of claim 20 wherein  $R_{2b}$  is -Cl.
29. The compound of claim 20 wherein  $R_8$  is a 3,5-disubstituted phenyl moiety, wherein both substituents are electron withdrawing groups.
30. The compound of claim 29 wherein both substituents are -CF<sub>3</sub>.
31. The compound of claim 29 wherein at least one of the substituents is -CF<sub>3</sub>.
32. The compound of claim 20 wherein  $R_{4b}$  is selected from -H, -CH<sub>3</sub>, -CF<sub>3</sub>, -CF<sub>2</sub>CF<sub>3</sub>, -C<sub>6</sub>H<sub>5</sub> and -CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>.
33. The compound of claim 20 wherein  $R_1$  is -H.
34. A composition comprising a compound of claims 1-33 and a pharmaceutically acceptable carrier or diluent.
35. A composition comprising a compound of claims 1-33 and a pharmaceutically or prophylactically acceptable carrier or diluent.
36. Use of a compound of claims 1-33 as an active therapeutic substance.



37. Use of a compound of claims 1-33 for the manufacture of a medicament for treating an inflammatory condition.

38. The use of claim 37 wherein the inflammatory condition is an immunoinflammatory condition.

39. The use of claim 38 wherein the immunoinflammatory condition is selected from rheumatoid arthritis, osteoarthritis, transplant rejection, sepsis, ARDS and asthma.

40. The use of claim 38 wherein the immunoinflammatory condition is rheumatoid arthritis.

41. The use of claim 37 wherein the inflammatory condition is an autoimmune disease.

42. The use of claim 41 wherein the autoimmune disease is selected from multiple sclerosis, psoriasis, inflammatory bowel disease, glomerulonephritis, lupus, uveitis and chronic hepatitis.

43. The use of claim 37 wherein the inflammatory condition is selected from trauma, oxidative stress, cell death, irradiation damage, ischemia, reperfusion, cancer and viral infection.

44. The use of claim 37 wherein the inflammatory condition is transplant rejection.

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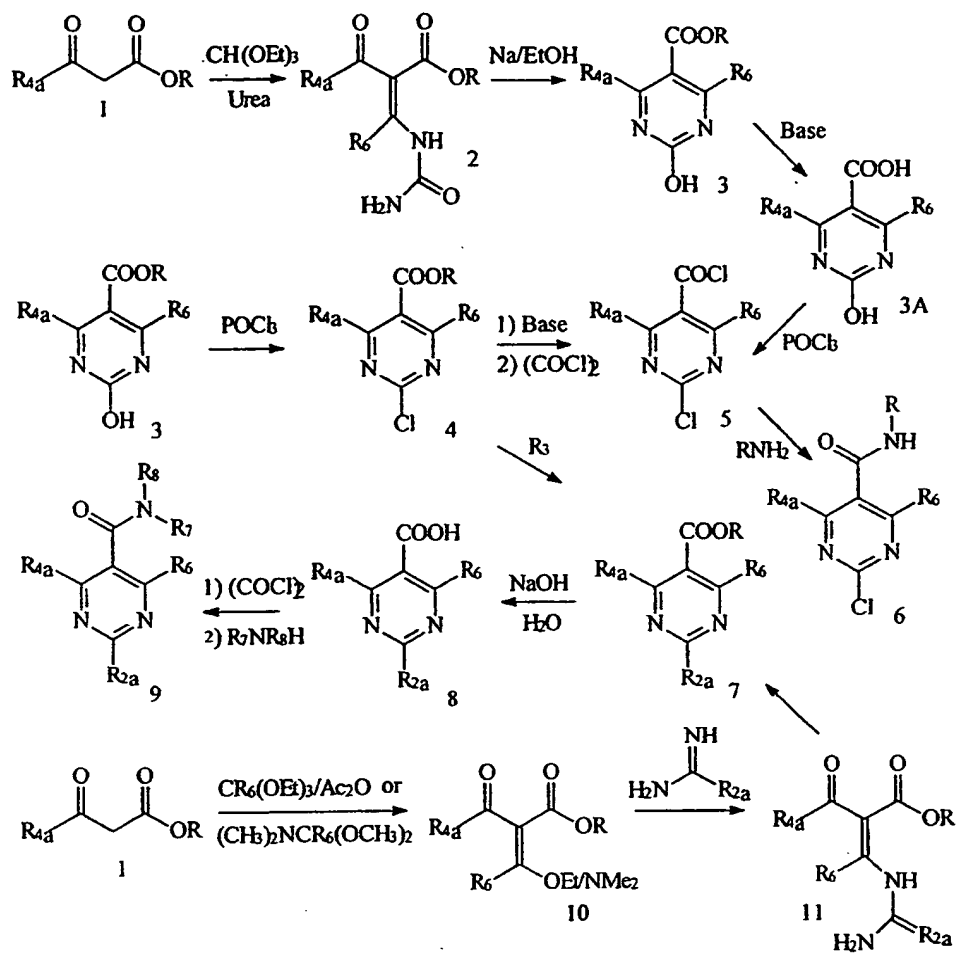
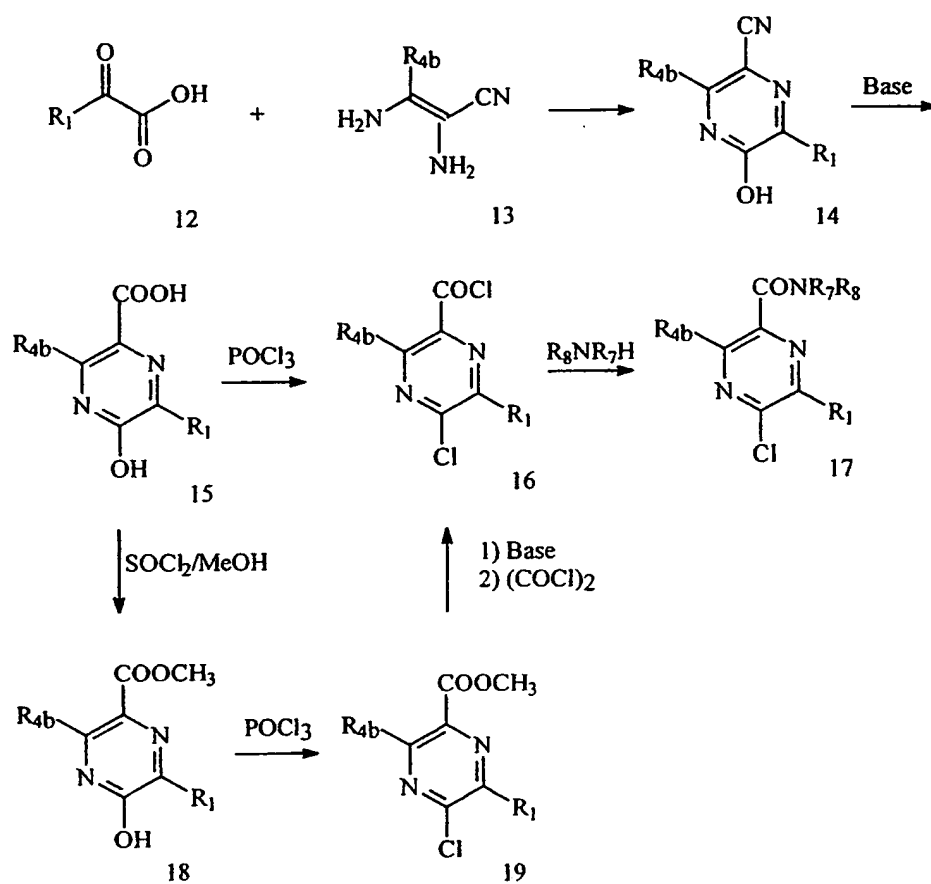
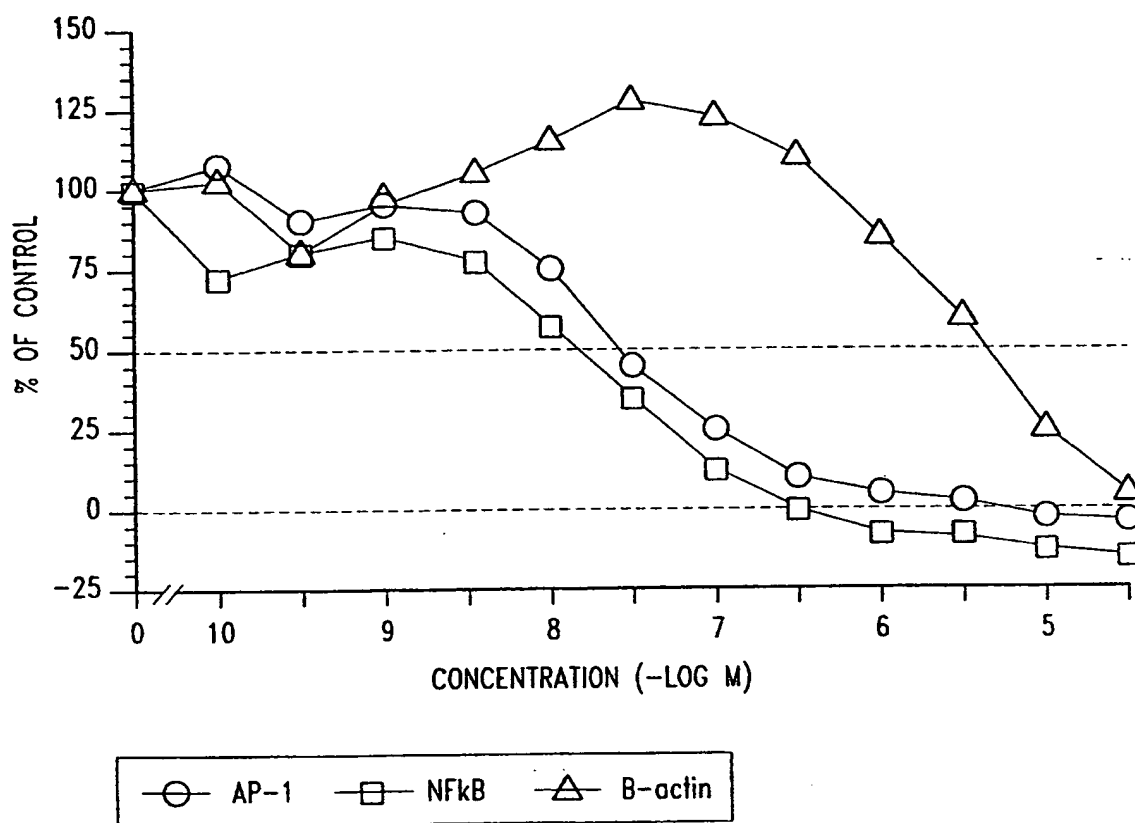


Fig. 1

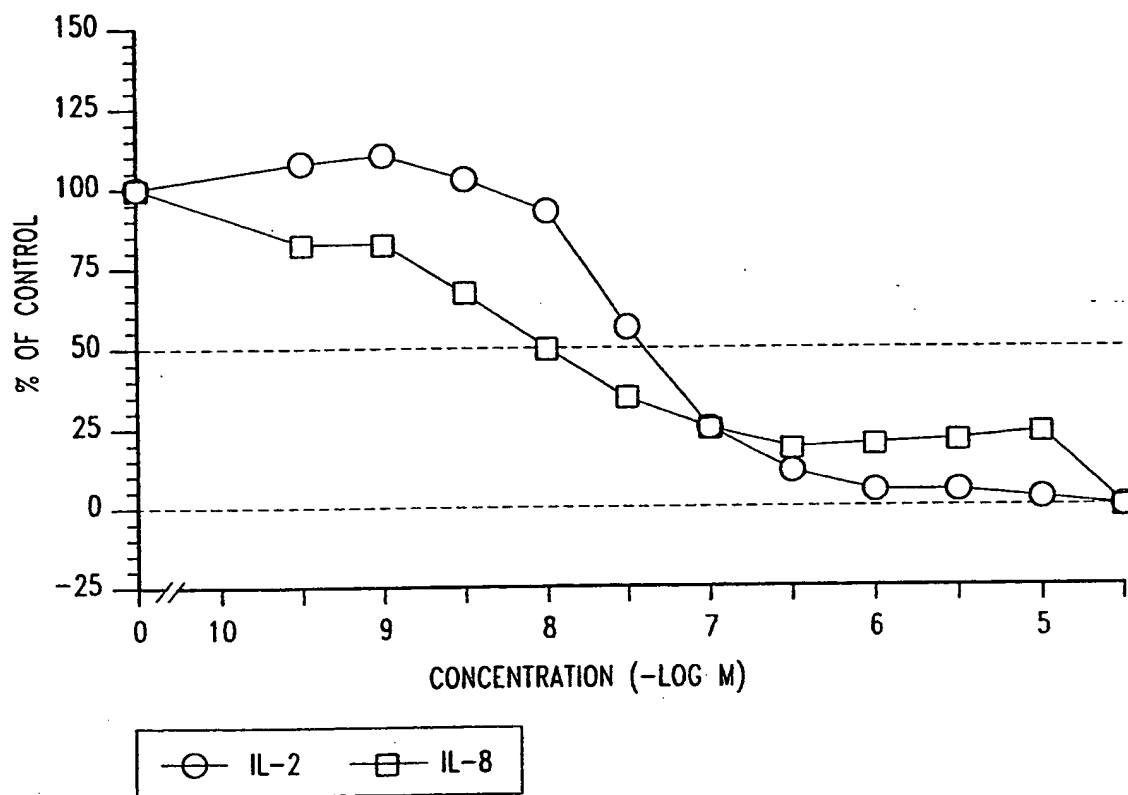
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*Fig. 2*

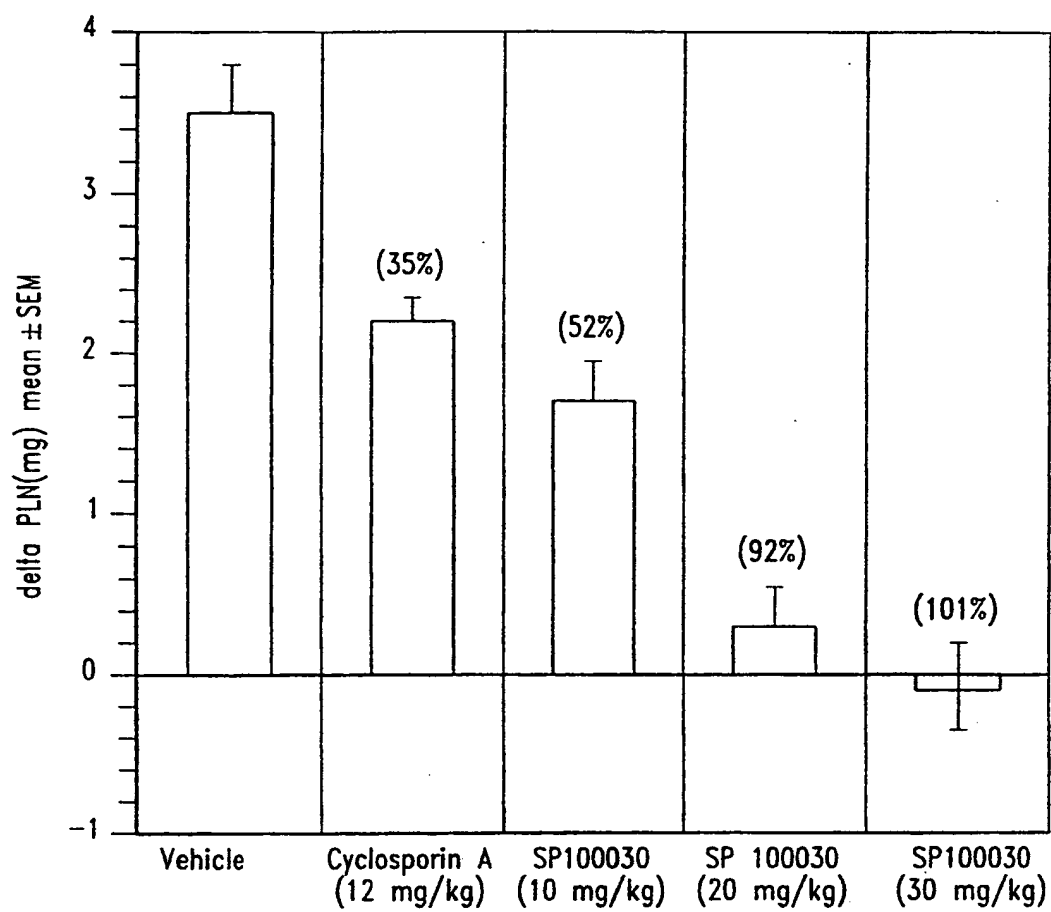
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*Fig. 3*

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*Fig. 4*

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*Fig. 5*

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US96/15108

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 6    C07D239/30    C07D239/28    C07D239/42    C07D241/24    C07D239/34 A61K31/505    A61K31/495		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 6    C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BE,A,489 416 (ROCHE) 3 June 1949  see claims; examples 6-10 ---	1-3,20, 34
A	EP,A,0 569 912 (HOECHST) 18 November 1993  see the whole document ---	1,7, 20-25
A	DE,A,32 05 638 (HOECHST) 25 August 1983  see page 28 - page 29; claims; examples 101-113; table 1 ---	1,7, 20-25
A	DE,A,29 06 461 (DELALANDE) 23 August 1979 see page 36 - page 49 ---  -/--	1
<div style="display: flex; justify-content: space-between;"> <span><input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.</span> <span><input checked="" type="checkbox"/> Patent family members are listed in annex.</span> </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents :</p> <p>* "A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>* "E" earlier document but published on or after the international filing date</p> <p>* "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>* "O" document referring to an oral disclosure, use, exhibition or other means</p> <p>* "P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>* "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>* "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>* "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>* "&amp;" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search  <div style="text-align: center; font-size: 1.2em;">20 December 1996</div>		Date of mailing of the international search report  <div style="text-align: center; font-size: 1.2em;">10.01.97</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016		Authorized officer  <div style="text-align: center; font-size: 1.2em;">Francois, J</div>

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US96/15108

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,3 517 010 (DONG H. KIM ET AL.) 23 June 1970 see column 1 - column 7 ---	1,34
A	US,A,3 517 009 (DONG H. KIM) 23 June 1970 see column 1 - column 6 ---	1,34
A	FR,A,2 139 411 (CIBA-GEIGY) 5 January 1973 see claims ---	1-3
P,X	WO,A,95 25723 (AGREVO UK) 28 September 1995 see the whole document ---	1,7,20, 25
A	CHEMICAL ABSTRACTS, vol. 109, no. 19, 1988 Columbus, Ohio, US; abstract no. 170451j, page 726; column 2; XP002021900 see abstract ---	1,34
A	& JP,A,63 107 966 (FUJISAWA) 12 May 1988 ---	1,34
A	CHEMICAL ABSTRACTS, vol. 110, no. 9, 1989 Columbus, Ohio, US; abstract no. 75558m, page 660; column 2; XP002021901 see abstract ---	1,7,20, 25
A	& JP,A,63 198 670 (DAICEL CHEMICAL IND.) 17 August 1988 ---	1,7,20, 25
A	CHEMICAL ABSTRACTS, vol. 112, no. 5, 1990 Columbus, Ohio, US; abstract no. 2621h, page 267; XP002021902 see abstract ---	1,7,20, 25
A	& JP,A,01 180 804 (DAICEL CHEM. IND.) 18 July 1989 ---	1,7,20, 25
A	CHEMICAL ABSTRACTS, vol. 112, no. 5, 1990 Columbus, Ohio, US; abstract no. 50609g, page 269; XP002021903 see abstract ---	1,7,20, 25
A	& JP,A,01 180 805 (DAICEL CHEM. IND.) 18 July 1989 ---	1,7,20, 25

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US96/15108

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EUROPEAN JOURNAL OF MEDICINAL CHEMISTRYCHIMICA THERAPEUTICA., vol. 17, no. 5, 1982, PARIS FR, pages 437-444, XP002021899 P.DOSTERT ET AL.: "STUDIES ON THE NEUROLEPTIC BENZAMIDES" see page 437 - page 443 ---	1,34-36
A	CHEMICAL ABSTRACTS, vol. 88, no. 3, 1978 Columbus, Ohio, US; abstract no. 22973p, page 644; column 1; XP002021907 see abstract -----	1,20,34, 36
A	& JP,A,07 783 679 (YAMANOUCHI PHARMA.) 12 July 1977 -----	1,20,34, 36

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US96/15108

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
BE-A-489416		NONE	
EP-A-569912	18-11-93	AU-A- 3855493 JP-A- 6032784 ZA-A- 9303373	18-11-93 08-02-94 09-12-93
DE-A-3205638	25-08-83	NONE	
DE-A-2906461	23-08-79	FR-A- 2417506 FR-A- 2457286 AU-B- 526298 AU-A- 4439279 BE-A- 874266 CA-A- 1096868 CH-A- 639078 GB-A, B 2014984 JP-A- 54130585 LU-A- 80937 NL-A- 7901333 SE-B- 446450 SE-A- 7901493 US-A- 4250178	14-09-79 19-12-80 06-01-83 19-07-79 20-08-79 03-03-81 31-10-83 05-09-79 09-10-79 29-10-79 23-08-79 15-09-86 22-08-79 10-02-81
US-A-3517010	23-06-70	NONE	
US-A-3517009	23-06-70	NONE	
FR-A-2139411	05-01-73	CH-A- 549339 DE-A- 2222729 NL-A- 7206347 US-A- 3845055	31-05-74 16-11-72 14-11-72 29-10-74
WO-A-9525723	28-09-95	AU-A- 1898195 ZA-A- 9502205	09-10-95 31-10-95